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sycosis barbae

10 out of 12 patients in one series[1]
22 out of 30 patients in another series[2]
responded to Vioform in sycosis barbae after penicillin had failed.[1,2]

1. *Martin-Scott, I.: Brit. Med. J.*, 1:837, 1949.
2. *Overton, J.: Brit. Med. J.*, 1:840, 1949.

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The Journal of Allergy

VOL. 22 NOVEMBER, 1951 NO. 6

Original Articles

PURPURA DUE TO FOOD SENSITIVITY

USE OF SKIN TESTING IN ETIOLOGICAL DIAGNOSIS

GIACOMO R. ANCONA, M.D., MATTHEW J. ELLENHORN, M.D., AND ERNEST H. FALCONER, M.D.*

OSLER[1] in 1914 suggested that purpuras might be manifestations of anaphylaxis. Since that time it has been reported that, in a considerable number of instances, purpuras of both the thrombocytopenic and nonthrombocytopenic types are of an allergic nature. As etiologic factors foods, drugs, inhalant allergens, and infections have been suspected. However, in many cases of purpura there is no evidence of an allergic nature and in others of possible allergic nature the specific allergens are difficult to recognize. The latter may be due to improper use of the available diagnostic procedures, but it is more probably the result of the inadequacies inherent in these methods.

At present there are four procedures which may aid in detecting the specific etiology of an allergic purpura: clinical history, skin tests, elimination of suspected allergens, and clinical trials. The use of other diagnostic methods, such as determination of the leucopenic index (Vaughan),[2] observation of the variation in the number of circulating platelets (Squier and Madison)[3] or rise in the pulse rate after ingestion of the specific allergens (Coca),[4] has not been generally adopted. Of the diagnostic procedures available to the clinician in his attempt to elicit the cause of an allergic purpura, the clinical history is probably the most valuable. A properly taken history in many cases has led to the discovery of the specific noxious substances. The skin tests, invaluable in the etiological diagnosis of other allergic manifestations, such as hay fever, have been found to be of less practical value when applied to the study of purpuras. The early investigators of the relation between purpura and allergy, including Duke,[5] Landsberger,[6] Alexander and Eyermann,[7, 8] Kahn,[9] Barthelme,[10] and Rowe,[11] found that positive skin reactions of clinical value were not common if skin testing with ordinary extracts was done by the scratch or intracutaneous methods. These results have been substantiated by numerous other observations in the last two decades, and the sensitivity or efficacy of skin testing has not been appreciably improved. The patch test method was used by Falconer and

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Schumacher[12] in 1940 to verify the etiologic diagnosis in a patient with thrombocytopenic purpura due to sensitivity to Sedormid,* with negative results.

More recently Donaldson and Scarborough,[13] and Ackroyd,[14] have applied the patch test technique in purpuras due to sensitivity to drugs and their results deserve further consideration. Donaldson and Scarborough performed patch tests with sulfathiazole in a patient suffering from nonthrombocytopenic purpura. Skin reactions of the usual eczematous type were not observed, but negative pressure applied by Scarborough's technique[15] to the sites of the patch tests revealed definite evidence of a reduced local capillary resistance. Ackroyd[14] investigated patients with thrombocytopenic purpura due to Sedormid. He was unable to obtain positive skin reactions with either the scratch or intracutaneous methods and could not demonstrate evidence of increased local capillary fragility after applying these tests. However, when Sedormid patch tests were applied, positive skin reactions and increased local capillary fragility were observed.

A third procedure, the elimination of suspected foods or drugs or the use of extensive elimination diets, has, in many cases, provided diagnostic clues. The final proof that a suspected allergen is the real offender can only be obtained by the fulfillment of Cooke's[16] postulates: the clinical manifestations should disappear after removal of the suspicious allergen and should be reproduced at will after proper exposure to it. The "provocative method of testing" is based on this concept. With its use one endeavors to reproduce the clinical symptomatology on a small scale by the controlled administration of small doses of the suspected allergen.

We have been able to study and follow a patient who exhibits a nonthrombocytopenic purpura due to sensitivity to crustaceans. The skin tests performed with foods in this individual have shown some peculiarities which, we believe, deserve to be reported. As a result of this study it is now apparent that the food testing materials containing crustaceans can be employed in a manner different from the usual skin testing routine used in the past. Moreover, the presence of multiple, antigenic fractions in some foods (crustaceans) recognized by Tuft and Blumstein,[17] has been reaffirmed and their properties established in relation to their presence or absence in fresh foods, frozen foods or commercial extracts.

CASE REPORT

H. T., a 30-year-old white, male teacher, was first seen on Dec. 28, 1947, because of ecchymoses on the back and legs associated with swelling of the left leg and foot.

He reported that on Christmas Eve he ate a salad which subsequently was discovered to contain minced crab and shrimp. On the following day he noticed that both ankles were swollen and covered with purpuric spots. Gradually the entire left leg and foot became swollen and purpuric spots appeared on both legs and on the back. The history revealed that this was his second attack of purpura. The first one had occurred in June, 1947 in Los Angeles, 12 hours after eating crab meat. At that time the attack began with petechiae on the right and left ankles and swelling of the left ankle. On the following day he noticed severe pain in the right flank and the passage of red urine. He was sent to a local hospital, where examination of the blood revealed a decrease in the number of blood platelets, a slight anemia, and a rapid sedimentation rate. A blood Wassermann test was negative. Vitamins E and C were administered. The hematuria ceased after he had been hospitalized for 9 days.

*Allyl-isopropyl-acetyl-carbamide, a sedative by Hoffmann-La Roche.

Later, in San Francisco, results of examination of the blood were normal. The blood Wassermann test was negative, and retrograde pyelograms were reported to be normal.

The patient stated that to the best of his knowledge he ate no crab meat between these two attacks.

The history revealed the following pertinent information: He had been in good health until the winter of 1939, when a sinusitis developed. He received numerous treatments for this condition, through the following years, and eventually was operated upon in 1942. A complete remission of the sinusitis followed for about one year.

In the summer of 1942, he developed his first attack of asthma which lasted about six weeks. The asthma recurred again during December of the following year.

In the spring of 1945 and 1946 he developed an oculo-rhinitis and at the height of the attack he had some asthma. No nasal symptoms were present after the patient moved from Los Angeles to Northern California in 1947. The asthma, however, recurred three more times, once in May and June, 1949, prior to the third attack of purpura; and again in November, 1949, without any purpuric manifestations.

In 1943, at the age of 23, he experienced an attack of generalized giant urticaria. This recurred approximately 6 times a year for the next 4 years. The duration of each episode was approximately one week, and relief was always spontaneous. He thought that the ingestion of fresh fruit, such as strawberries or peaches, was responsible for the urticaria. Apparently, however, he could eat such fruits cooked or canned without harmful sequelae.

There has been no other abnormal skin manifestation except the subsequent purpura and a recurrent tinea pedis, and no history of any other manifestation which might be related to allergy.

One paternal uncle and a paternal aunt had asthma and dermatitis, possibly from sensitivity to shell fish.

The physical examination revealed a somewhat obese young man in no apparent pain, but with moderately labored respiration and obviously prolonged expiration. Examination of the skin revealed large ecchymotic areas on the back and legs. There was a mild left epitrochlear adenopathy. The chest was emphysematous. There was a prolonged expiratory note with moderate wheezing throughout both lung fields. The heart was of normal size by percussion. The rhythm was normal. There were no murmurs. Abdominal examination revealed the spleen to be palpable on deep inspiration. The liver was not palpable. There were no other abdominal masses. The left leg and foot were swollen and the left calf was tender. An examination of the blood at this time revealed: hemoglobin 13.8 Gm., red blood cells, 4,580,000 per cu. mm.; platelets 180,000; white blood cells 7,300. A differential count revealed neutrophils 68 per cent (filaments 61, non-filaments 7), eosinophils 2, lymphocytes 26 and monocytes 4. The icterus index was 7.5 units, the sedimentation rate (Wintrobe corrected) 4 mm. per hour and the prothrombin concentration 102 per cent. The nasal secretion showed a large number (4 plus) of eosinophiles. A sternal marrow puncture was performed with the following differential count of the smear:

Promyelocytes	1.8
Myelocytes-neutrophilic	10.8
Myelocytes-eosinophilic	8.6
Metamyelocytes-neutrophilic	4.0
Polymorphonuclear neutrophils filamented	1.4
Polymorphonuclear nonfilamented	21.4
Polymorphonuclear eosinophils	5.6
Lymphocytes	8.6
Plasmacytes	4.8
Proerythroblasts	0.6
Erythroblasts	28.8
Megakaryocytes	3.6
Total	100 per cent

The megakaryocytes were seen to be budding a normal number of platelets from their cytoplasm. The smear was interpreted to be within normal limits. On Jan. 7, 1948, the platelets were 240,000 per cu. mm.

The patient was free of purpura until the end of June, 1949, when he again ate some shrimp and crab. Forty-eight hours later he noted hemorrhagic skin lesions over the face, neck, scrotum and lower part of the legs. A blood count at that time was reported as essentially within normal limits.

Shortly after leaving his doctor's office, and upon returning home, he experienced a hemorrhage in the muscles of the buttock and about the hips which forced him to remain in bed for 2 weeks. He was given Neoantergan and Pyribenzamine, but purpuric skin manifestations continued to be present.

On August 2, 1949, he exhibited an ecchymosis, 6 by 8 cm., on the dorsum of the left foot. Several small areas of ecchymosis were seen on the right foot and ankle. Many ecchymoses, varying from 2 mm. to 5 mm. in diameter, were noted about the scrotum, over the perineum and inner aspects of the thighs, some of which were ulcerated from scratching. A hard, tender area, 3 by 4 cm., probably a fibrosed hematoma, was present in the left posterior cervical triangle, and caused some pain. The spleen was palpable at the left costal margin and was not tender. At this time the blood count was essentially normal. The blood platelets were 310,000 per cu. mm. The bleeding time was 3½ minutes. A sternal marrow puncture revealed little change from the specimen of marrow previously obtained. The clotting time was 10 minutes, and the clot showed good retraction at 3 hours. A heparin protamine titration was within normal limits.

The patient was hospitalized for a short period, during which time the severity of the lesions decreased considerably. He was given rutin, Neoantergan and Benadryl with subsequent clearing of the crural ecchymotic areas. A capillary fragility test on Aug. 20, 1949, showed 20 petechiae when a negative pressure of 10 mm. Hg was applied to the right antecubital fossa for one minute. He continued to note some edema of the ankles at the end of the day.

On Sept. 13, 1949, after discharge from the hospital he still had slight edema of the ankles, but by November, 1949, the edema had subsided. Capillary fragility was definitely increased.

It was during this period that a series of skin tests was performed with a large number of commercial extracts of pollens, fungi, epidermals and miscellaneous inhalants by the scratch and intracutaneous methods. Positive reactions were elicited with the pollens of most of the grasses. These were considered to be of clinical value, since they correlated well with the seasonal recurrences of asthma and hay fever as reported by the patient.

Skin tests with foods were made with a large series of commercial extracts by the scratch and intracutaneous methods; with 50 raw frozen foods by the scratch method; and with a few fresh foods suggested by the history, including crab, prawns, strawberry, and peach, by scratch method.

The use of frozen raw foods as a skin testing material has recently been introduced. Ancona and Schumacher[18] have emphasized that greater sensitivity and potency are demonstrated with these materials than with the commercial extracts.

Positive skin reactions (Table I) were obtained by scratch testing with fresh, frozen, and boiled crab meat. No positive reactions were obtained with the commercial extracts of crab and other crustaceans from three different reputable manufacturers when the scratch as well as the intracutaneous methods were used.

Patch tests were performed with fresh, frozen and boiled crab meat and with the very same three commercial crab extracts which had not induced positive skin reactions by either the scratch or intracutaneous methods. At the end of 24 hours the reading showed strong positive reactions characterized by erythema, edema, vesiculation and petechiae.

Passive transfer tests were done in order to prove the presence in the serum of skin-reacting antibodies to crab. The sensitized sites when tested with a variety of fresh* and commercial extracts by the intracutaneous and patch test methods showed uniformly negative results.

Simultaneous controls were run in allergic and nonallergic individuals. All the positive skin tests were repeated and showed the same positive results.

TABLE I. SKIN TESTS WITH CRAB

TYPE OF MATERIAL USED	METHODS USED				
	DIRECT			PASSIVE TRANSFER	
	SCRATCH	INTRACUTANEOUS	PATCH	INTRACUTANEOUS	PATCH
Fresh raw	positive	–	positive	negative	negative
Fresh boiled	positive	–	positive	negative	negative
Frozen raw	positive	–	positive	negative	negative
Commercial extracts					
manufacturer I powder	negative	–	positive	–	negative
manufacturer II powder	negative	–	positive	–	negative
manufacturer III glycerinated	negative	–	positive	–	negative
manufacturer III aqueous	–	negative	–	negative	–
manufacturer IV aqueous	–	negative	–	negative	–

Table I summarizes the results of the various types of skin tests performed with crab. Prawns, because of their common antigenic properties with crab (Tuft and Blumstein),[19] produced similar results. The skin tests positive to crustaceans were considered of clinical value in indicating the cause of the purpura, and therefore the patient was advised to avoid ingestion of all crustaceans. At the present time, nineteen months from the last attack, no purpuric manifestations have developed. Diagnostic ingestion tests (provocative tests) were not performed. These tests were believed to be of great danger to the patient since the clinical manifestations during his last attack had been very severe and it would have been too difficult to foresee accurately the degree of reaction to the ingestion of even a small amount of crab. It was believed, moreover, that the clinical history, the results of the skin tests, and the subsequent clinical course had given sufficient proof of the etiological diagnosis of the purpura. The specific factors responsible for the occurrence of the urticaria or for the asthma in the wintertime could not be positively identified.

DISCUSSION

The analysis of Table I allows some speculation on the results of the skin tests.

Raw, frozen, boiled, or autoclaved crab meat induced positive reactions by the scratch method, although the usual commercial crab extracts prepared by

*For the intradermal testing of the passively sensitized sites, exclusively, a crab meat extract was prepared as follows: Fresh raw crab meat was reduced to pulp, mixed with an equal volume of distilled water, extracted for two hours at refrigerator temperature and then centrifuged. The supernatant fluid, after passage through a Swinny filter, was used immediately for testing. This extract was obviously a crude one, and the possibility of loss of potency through filtration was considered.

several reputable firms failed to give positive reactions by the scratch or even by the intradermal method. All the crab materials, i.e., raw, raw frozen, boiled, autoclaved, and powdered or glycerinated commercial extracts had in common the property of eliciting positive skin reactions to patch tests. This would appear to indicate the existence of two antigenic fractions in crab meat: one fraction present in the fresh raw, raw frozen, boiled, or autoclaved meat is apparently thermostabile and is absent in the commercial extracts. It is possible that this fraction may either have been retained in the Seitz filtration used by most of the manufacturers or suffered deterioration in time at room temperature. Similar results were reported in 1942 by Tuft and Blumstein[19] for the antigens present in some fresh fruits. However, the labile fraction present in the fruits was destroyed by canning or cooking, while this first fraction present in crab meat exhibited thermostability.

The results of the patch tests were all positive no matter what type of crab material was used, fresh, frozen, cooked, or commercial extract. This observation suggests that all these testing materials contain a second antigenic fraction which, although unable to provoke positive reactions by scratch tests in our patient, elicited the positive reactions in the patch tests. This second antigenic fraction also appears to be thermostabile, but unlike the first fraction, it does not lose its potency through the various steps of extraction, filtration and drying encountered in the manufacture of the commercial extracts. Moreover, this fraction in powder form as well as in glycerinated solution maintains its activity for years at room temperature.

CONCLUSIONS

1. A patient with nonthrombocytopenic purpura has been studied. History, skin tests and subsequent course point to the allergic nature of his condition. The specific allergen has been recognized as meat of crustaceans (crab).

2. Once more it has been demonstrated that the use of fresh, raw and frozen crab or shrimp meat in tests by the scratch method is more apt to detect a specific state of sensitivity than the use of corresponding commercial extracts by the same scratch method or even by the intracutaneous method.

3. The use of foods as materials for patch tests has been found of diagnostic aid and is recommended in the search for the etiological diagnosis of purpuras.

4. The presence of at least two antigenic fractions in the meat of crustaceans has been suggested by the results of the skin tests performed with raw fresh or raw frozen or cooked material as compared with those using the corresponding commercial extracts. The characteristics of these antigenic fractions have been discussed.

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BRONCHIAL ASTHMA, URTICARIA, AND ALLERGIC RHINITIS FROM TANNIC ACID*†

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RECENTLY one of us (A. G. C.) had the opportunity to investigate a patient who had shown definite allergic manifestations to tannic acid. We believe the case to be important in that it is a clear-cut example of sensitivity to an antigen, either complete or hapten, of simple, non-nitrogenous structure and low molecular weight. To the best of our knowledge this is the first case in which a hydrolytic product of a simple, naturally occurring, non-nitrogenous compound gave immediate whealing reactions by the scratch and passive transfer methods.

CASE REPORT

M. L., a 24-year-old white man, received a mild burn on his foot in 1940 which was treated with a tannic acid solution. This burn took about three months to heal. A short time later he began having nasal symptoms of rhinorrhea, sneezing, nasal obstruction, and itching of the nose. The patient was first seen in 1942 with symptoms of rhinorrhea, sneezing, nasal obstruction and itching of the nose, mostly in the summer months. An extract of alternaria, ragweed, and dust was given at intervals but any improvement was attributable to symptomatic medication as he was never treated for more than a few weeks at a time. In 1949, while in Florida, he had an attack of severe rhinitis and urticaria immediately after using a tannic acid paste for sunburn.

In early July, 1950, the patient was seen as a home emergency with severe bronchial asthma and generalized urticaria. He attributed the attack which had come on suddenly to the use of a sunburn spray containing tannic acid. The label stated that the active ingredients were tannic acid, chlorobutanol, and alcohol. On July 10, 1950, severe asthma and generalized urticaria occurred 20 minutes after a scratch test to this spray which gave a markedly positive reaction with a wheal 25 mm. in diameter. This required two injections of 0.3 ml. of 1:1,000 epinephrine hydrochloride 15 minutes apart for relief. He was completely free of asthma almost immediately, but the urticarial lesions persisted over his shoulders four hours after the onset. The following day tea was omitted from his diet as this beverage contains up to 11 per cent tannic acid. (1) On July 19, 1950, a scratch test to a strong solution of tea produced an immediate whealing reaction, 11 mm. in diameter appearing within five minutes. On August 7, 1950, he reported that his allergic rhinitis had improved. A glass of tea was given at 10:00 A.M. and within a few minutes he developed a "chugging around" in his stomach. At 12:30 P.M. he had another glass of tea and an hour and a half later he had an attack of asthma sufficiently severe to require epinephrine for relief. The patient recalled that his allergic rhinitis had been worse in summer when he drank iced tea. On Sept. 23, 1950, another severe attack of asthma occurred, requiring epinephrine for relief. The patient was unable at this time to account for the attack. On Oct. 17, 1950, while at work, he again developed a severe asthmatic attack requiring epinephrine hydrochloride for relief. At the time of this attack he was watching workmen at the shop setting a saw for cutting cross ties which were made of oak lumber. He then recalled that at the time of the previous attack for which

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†This investigation was made possible, in part, through the generosity of Mr. L. J. Montgomery of Las Vegas, Nevada.

he had been unable to ascribe a cause, he had been watching workmen making shelves. Subsequent inspection proved that these shelves were made of oak. Oak lumber is known to contain a large amount of tannic acid.[2] Since Oct. 17, 1950, by avoiding known sources of contact with tannic acid he has had no asthma and only mild nasal symptoms to date. The family history was known to be positive for allergy in that a sister had severe ragweed hay fever. Skin tests on the patient by the scratch method showed mild reactions to ragweed, grass, alternaria, and house dust.

LABORATORY AND IMMUNOLOGIC STUDIES

The patient was scratch tested with a 1:1,000 solution of tannic acid which gave a marked whealing 11 mm. in diameter in 5 minutes. A solution of egg albumin was added to a solution of tannic acid in excess of the maximum precipitate. The precipitate was washed with water, dissolved in slightly alkalinized solution, and a scratch test was made with this solution of egg albumin tannate. It produced a rapid whealing response on the subject. Scratch tests to a crude extract of the saw dust collected from the aforementioned oak lumber produced an immediate type of whealing reaction.

Ten nonallergic subjects gave negative reactions by the prick test to U.S.P. tannic acid in a dilution of 1:3. Using a 1:1,000 dilution of U.S.P. tannic acid by the intradermal technique mild nonspecific reactions occurred. Undoubtedly such reactions are related to impurities in U.S.P. tannic acid or to the irritating quality known to be characteristic of the tannic acid itself.[2]

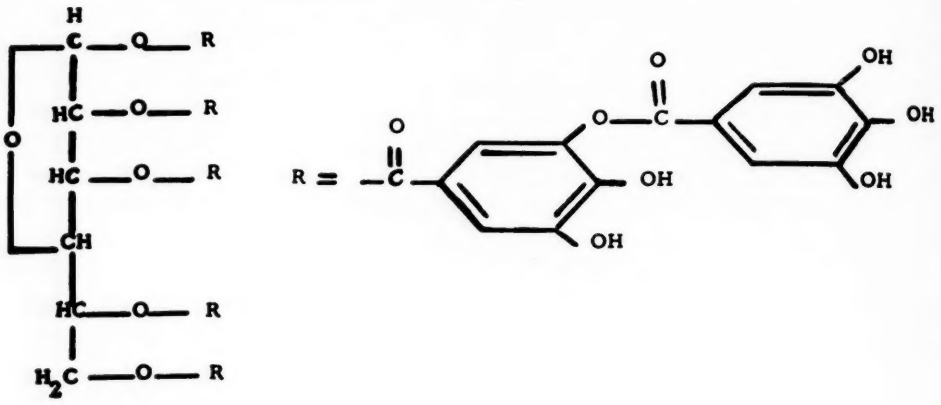
Prausnitz-Küstner[3] tests on 12 subjects in which serum was injected and tested after 48 hours with 0.025 ml. of U.S.P. tannic acid in dilutions of 1:1,000, 1:10,000, 1:100,000 and 1:1,000,000 gave an immediate whealing response in all subjects which persisted 20 minutes after the control site reaction had disappeared. Prick tests to the passive transfer sites with a dilution of 1:3 tannic acid gave an immediate whealing response with negative controls.

Pure, reagent-grade tannic acid was obtained from two separate manufacturers in order to rule out the possibility of impurities in the U.S.P. tannic acid as the cause of the positive Prausnitz-Küstner tests previously observed. Passive transfer tests of 12 persons all gave good positive reactions to dilution up to and including 1:1,000,000. The dilution of 1:10,000,000 was negative in the one case on whom it was tried. Passive transfer sites in two instances were exhausted by two injections of 0.025 c.c. of 1:1,000 reagent tannic acid. One subject required three injections of 0.025 c.c. of 1:1,000 reagent tannic acid before exhaustion occurred. The patient's serum diluted 1:2, 1:4, 1:8, 1:16, 1:32, 1:64 and 1:100 gave immediate whealing responses with 0.025 c.c. of a 1:1,000 dilution of reagent tannic acid in 48 hours. When tested with 0.025 c.c. of the patient's serum diluted 1:1,000 a two-plus reaction was obtained.

In an attempt to find out whether or not breakdown products of tannic acid (Fig. 1) would also give positive Prausnitz-Küstner reactions we tried gallic acid (Fig. 2) which is produced by hydrolysis of tannic acid. Six control subjects were injected with 0.05 c.c. serum from the allergic patient and 0.025 c.c. of 1:1,000 solution of gallic acid was injected into the sites two days later. Transfer sites gave a good positive wheal in five out of six subjects, while control sites were negative. Gallic acid, prepared one month before testing, failed to

give a positive passive transfer reaction on one occasion. Passive transfer sites were exhausted by one to three injections of 0.025 c.c. of freshly prepared gallic acid.

Resorcinol (Fig. 3) injected into transfer sites failed to produce an immediate whealing reaction in four persons in whom it was tried. Pyrogallol (1, 2, 3 trihydroxybenzene—Fig. 4) gave a positive Prausnitz-Küstner reaction in one out of three cases on whom it was tried, while 1:1,000 pyrogallol triacetate (Fig. 5) and pyrogallol 1, 3 dimethyl ether (Fig. 6) 1:1,000 gave negative reactions when injected into transfer sites in all three patients tested.



TANNIC ACID

Fig. 1.—The structural formula of tannic acid, a pentadigalloyl esterlike compound of glucose, $C_{76}H_{52}O_{46}$; Molecular weight 1700.

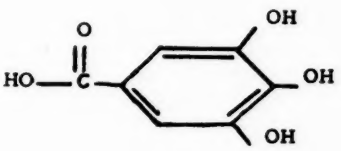
CHEMISTRY OF TANNIC AND GALLIC ACID

Tannic acid U.S.P.[2] is a yellowish-white amorphous bulky powder with a faint characteristic odor and astringent taste. It is a natural product occurring in the bark and fruit of many plants, the commercial source being Turkish or Chinese nutgalls and is produced when the galls are fermented under special conditions and then extracted with water saturated ether. Emil Fischer[4] established the structure of tannic acid as a pentadigalloyl esterlike compound of glucose. $C_{76}H_{52}O_{46}$; molecular weight 1700 (Fig. 1). Tannic acid gives insoluble precipitates with albumin, starch, gelatin, most alkaloidal and metallic salts. These precipitates may be dissolved by alkaline solutions. Tannic acid solution quickly combines with a soluble protein forming a tannate which is relatively stable, and insoluble in water. It is partially soluble in alkaline solutions.

Gallic acid, a product of the hydrolysis of tannic acid, forms colorless, odorless prisms which melt with decomposition at 225-250° C. It has been identified as trihydroxy benzoic acid, $C_7H_6O_5$,[4] molecular weight 170 (Fig. 2).

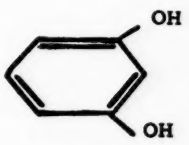
Attempts to Sensitize Guinea Pigs to Tannic Acid.—To the best of our knowledge no attempts to sensitize animals to tannic acid have yet been reported,

but in an experiment by one of us (H. N. M.), six guinea pigs were given subcutaneously 0.10 ml., 0.20 ml., 0.30 ml., 0.50 ml., 0.75 ml., and 1.0 ml. of a seitz-filtered aqueous 1 per cent solution of U.S.P. tannic acid. No abnormal manifestations except localized cutaneous erythema were seen as the result of this treatment. Two days later, the same animals were given enough tannic acid solution to make the total received 1.1 ml. Fourteen days later, a single intracardiac injection of 0.10 ml. of the original tannic acid was given each animal. No effect was noticed immediately, nor for the six weeks following. The same procedure was repeated using a new set of six pigs with the same results.



GALLIC ACID

Fig. 2.

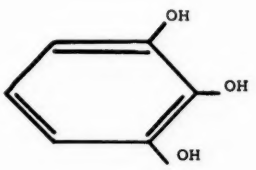


RESORCINOL

Fig. 3.

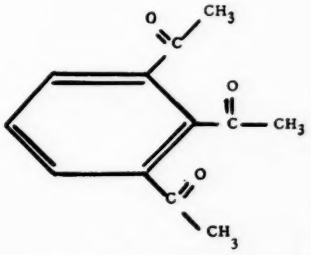
Fig. 2.—The structural formula of gallic acid, trihydroxybenzoic acid, $C_7H_6O_5$; molecular weight 170.

Fig. 3.—The structural formula of resorcinol 1,3; dihydroxybenzene.



PYROGALLOL

Fig. 4.



PYROGALLOL TRIACETATE

Fig. 5.

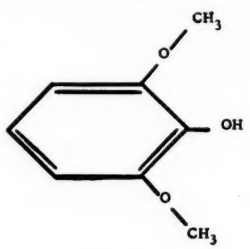
Fig. 4.—The structural formula of pyrogallol 1, 2, 3; trihydroxybenzene.

Fig. 5.—The structural formula of pyrogallol triacetate.

Attempts to Sensitize Guinea Pigs to Protein Tannate.—Freshly separated guinea pig serum was precipitated with a slight excess of 1 per cent tannic acid solution. The precipitate was removed by centrifugation, washed once with slightly acid water, and redissolved in water made slightly alkaline by a drop of NaOH solution and adjusted to equal the volume of serum originally used. Six guinea pigs were given two subcutaneous injections of 0.1 ml. of this preparation on alternate days. Fourteen days later, a single 0.10 ml. intracardiac injection of (a) serum protein tannate or (b) normal untreated guinea pig serum was made. In neither case was any degree of anaphylaxis observed. This procedure was repeated using a new set of six pigs with the same result.

THE SOURCES OF CONTACT AND USES OF TANNIC ACID[5, 6]

Tannic acid is found: in various concentrations in the bark or fruit of most plants; in various species of oak, hemlock, and sumac; in myrobalen, chestnut bark, and coconut fiber; in some perfumes for color and astringency; in sunburn lotions and ointments; in solutions in the treatment of bed sores; in some douche powders, in almost all fruits, vegetables, nuts, and fibrous foods; in the manufacture of ink; in some hemorrhoidal ointments; in antidotes to some metals; in some medicines for diarrhea; in the leather industry for tanning leather; in detoxifying diphtheria toxin; in combination within insulin to prolong its action; with barium sulfate in x-ray studies of the gastrointestinal tract; in some astringents, some syptics, and in some antiseptics; and in some enemas for the treatment of bacillary, amebic, or flaggelate dysentery. According to the American Institute of Cleaners and Dyers, tannic acid is a source of much permanent staining of clothing in spilled fruit juice stains. Tea, coffee, and cocoa contain an appreciable quantity of tannic acid, although they do not serve as commercial sources. Green tea may contain up to 11 per cent tannic acid.[1]



PYROGALLOL
1, 3 - DIMETHYL ETHER

Fig. 6.—The structural formula of pyrogallol 1, 3; dimethyl ether.

DISCUSSION

On the day following direct skin tests with the tannic acid spray mentioned above, July 11, 1950, both skin test sites were raised, indurated, brawny and 33 mm. in diameter. There was no vesiculation or desquamation. The reaction disappeared in 72 hours. The possibility has been suggested that this might be the missing link between atopic and contact reactions.

The passive transfer reaction seems specific for the trihydroxyphenyl structure of tannic acid and gallic acid since the dihydroxyphenyl compound, resorcinol, gave a negative result.

Tannic acid appears to be the allergen or hapten which is capable of producing asthma, urticaria and allergic rhinitis, as well as gastrointestinal symptoms in this case. It presumably has induced the formation of a large amount of antitannate reagin. The severity of the symptoms caused by the minimal degree of exposure to tannic acid has produced a degree of sensitivity in this case equal to that of other known allergens.

To the best of our knowledge sensitivity to tannic acid or gallic acid has not previously been reported. Nor have other allergens on hydrolysis produced compounds of such small molecular weight which were capable of demonstration by direct and passive transfer tests.

SUMMARY AND CONCLUSIONS

1. A case of allergy to tannic acid and gallic acid is reported.

2. Symptoms have occurred from both ingestion and inhalation to tannic acid.

3. The presence of antibodies to tannic acid and gallic acid has been demonstrated by means of direct skin testing and by the Prausnitz-Küstner technique.

4. The fact that reagins have been demonstrated to both tannic acid and gallic acid and were absent to resorcinol would suggest that the antigen in our patient has a trihydroxyphenyl configuration.

5. The fact that simple chemical compounds such as tannic acid and gallic acid can be potent allergens raises the question of the possibility of other simple chemicals as the etiological cause for heretofore unexplained allergic diseases.

The authors wish to express their appreciation to Dr. Charles H. Eyermann for additional confirmation of the passive transfer reaction to tannic acid and for many helpful suggestions.

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THE SIGNIFICANCE OF THE ANTISTREPTOLYSIN TITER IN RESPIRATORY ALLERGY*

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WITH THE TECHNICAL ASSISTANCE OF CAROL FEUERPFEIL

THE Lancefield Group A hemolytic streptococcus[1] liberates, among other substances, a hemolyzing agent or streptolysin. Todd[2] identified a streptolysin S and a much more antigenic streptolysin O. The antibody for streptolysin O is readily measurable and several methods for its determination have been developed.[3-6] The antistreptolysin is a specific antibody of the hemolytic streptococcus[7] and according to Mote and Jones[8] is not increased in infections in which the streptococcus has been excluded. It has been observed that 85 to 90 per cent of patients infected with Group A hemolytic streptococci responded with an increased streptolysin antibody index in the convalescent period.[8, 9] The anamnestic response of the antistreptolysin to nonspecific bacterial stimulation is not of major significance. Administration of typhoid vaccine to ten 14-year-old girls with rheumatic mitral stenosis did not provoke a rise in the antistreptolysin titer 7 and 14 days following the inoculation.[10] The antistreptolysin level was not altered in an epidemic of influenza among a group of rheumatic subjects.[3] A number of reports have shown that the antistreptolysin titer was not significantly influenced in pneumococcal pneumonia.[10-13]

It appears, therefore, that the demonstration of significant amounts of antistreptolysin in human sera offers convincing evidence of a streptococcal infection, and this has been used to corroborate a diagnosis of rheumatic fever.[3, 7, 12, 14, 15, 16] It has been only in rheumatic fever that this particular immunologic reaction has been studied intensively. However, reports of Cavelti,[17] Swineford and Holman,[18] Harkavy,[19] and others emphasizing the importance of bacterial sensitization, particularly in regard to the hemolytic streptococcus, justify application of the same principle to other diseases caused by bacterial allergy. To our knowledge no attempt has been made to correlate abnormal antistreptolysin titers with respiratory allergy. We have undertaken such a study although we fully realized that the applicability of this immunologic procedure was limited. Our aims were to note the incidence of elevated antistreptolysin indices in atopic and infectious respiratory allergy, to observe the duration of the elevation and to evaluate if possible its significance in bacterial allergy.

METHODS OF STUDY

Classification of Patients.—Patients were placed in the following categories: (1) atopic rhinitis; (2) bronchial asthma, atopic; (3) bronchial

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asthma, infectious; (4) bronchial asthma, atopic and infectious; (5) bronchial asthma, indeterminate. Those manifesting a combination of atopic rhinitis and atopic asthma were classified with group 2.

Allergic Study.—After a comprehensive history and a complete physical examination with special emphasis on the nasopharynx, each patient was tested with the common foods and inhalants. Cutaneous testing was followed by intracutaneous testing, especially with inhalants, for detection or confirmation of suspected atopic sensitivities. Mucous membrane tests and, in a few instances, passive transfer studies were done when deemed necessary.

Antistreptolysin Titration.—The antistreptolysin titer was determined by the method described by Rantz and Randall.[5] In brief, streptolysin was prepared from a culture of Group A hemolytic streptococci,* sterilized, and stored in the oxidized form. It was reduced to its active state just prior to performance of the test. The combining unit was determined by incubating serial dilutions of lysin and 1 ml. of standard antistreptolysin (containing 1 unit per ml.) and a 5 per cent suspension of sheep red cells. The combining unit was indicated by the tube which just fails to show hemolysis. The antistreptolysin index was determined in a similar manner except that sheep cells were added to tubes containing, in addition to the other ingredients, serial dilutions of patient's serum instead of standard antistreptolysin. The tube just failing to show hemolysis represented the titer in units per milliliter (Table I). A reading of 250 units or above was considered significant. A titer of 100 to 166 units bore no clinical significance but indicated that serial studies should be undertaken.

TABLE I. DETERMINATION OF THE ANTISTREPTOLYSIN TITER[5]

	SERUM DILUTION											
	1:10		1:100					1:500				
Ml. diluted serum	0.8	0.2	1.0	0.8	0.6	0.4	0.3	1.0	0.8	0.6	0.4	0.2
Ml. isotonic buffer	0.2	0.8	0.0	0.2	0.4	0.6	0.7	0.0	0.2	0.4	0.6	0.8
Ml. reduced lysin	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Unit value each tube	12	50	100	125	166	250	333	500	625	833	1250	2500

Special efforts were made to measure the amount of serum antistreptolysin at least twice in each individual. Because contact with some of the patients was lost, these attempts were not always successful. The number of titrations made for each individual depended on the availability of the patient, the nature of the disease, and the degree of the antistreptolyisn response. Those with infectious bronchial asthma received the greatest attention. Those with elevated levels were tested frequently to gauge the constancy and fluctuation of the antistreptolysin.

Culture Study.—Blood agar and brain-heart broth were used as media for throat swabs and sputum specimens. Culture inoculations were done at varying intervals to isolate or investigate the persitence of the hemolytic streptococcus. That the recovery of the organism is not a simple matter is attested by the reports of Rantz, Jacobs, and Kirby[20] and the Commission on

*Through the kindness of Dr. Rebecca C. Lancefield.

Acute Respiratory Diseases.[21] Accordingly, failure to recover the hemolytic streptococcus was not necessarily conclusive evidence of absence.

Other laboratory examinations included peripheral blood examinations for eosinophilia, nasal and sputum smears for the detection of eosinophils, and roentgenograms for chest and sinus pathology.

RESULTS

Four hundred fifty-five titrations were made from 160 patients. A titer of 250 units or more per milliliter was considered significant. Five of 27 patients with atopic rhinitis had increased antistreptolysin titers but none maintained a continued elevation (Table II). Similarly, in the atopic bronchial asthma group and in the group of asthmatic patients in whom the etiologic factor was undetermined, there were transitory elevations but no prolonged increase of the antistreptolysin titer. In the group of cases classified as infectious bronchial asthma, 14 of 43 patients, or 32.5 per cent, demonstrated antistreptolysin elevations and 4 had sustained abnormal titers. In the atopic-infectious bronchial asthma group 8 of 35 patients, or 22.8 per cent, had increased antistreptolysin levels; 5 had prolonged elevations. Table III shows, in months, the duration of the abnormal antistreptolysin response of the 9 asthmatic patients who persistently demonstrated an increased titer. The period of abnormal antistreptolysin response ranged from a few months to 2½ years.

TABLE II. SUMMARY OF ANTISTREPTOLYSIN DETERMINATIONS

GROUP	NUMBER OF PATIENTS	NUMBER OF TESTS	PATIENTS WITH TITER ABOVE 166 UNITS		PROLONGED HIGH TITER	
			NUMBER	PER CENT	NUMBER	PER CENT
1. Atopic rhinitis	27	60	5	18.5	0	
2. Atopic bronchial asthma	45	110	13	28.8	0	
3. Infectious bronchial asthma	43	149	14	32.5	4	9.3
4. Atopic-infectious bronchial asthma	35	106	8	22.8	5	14.2
5. Bronchial asthma, unidentified	10	30	1	10.0	0	
Totals	160	455	41	25.6	9	11.5*

*Of 78 patients in Groups 3 and 4.

Of 11 patients who had a history of scarlet fever and/or rheumatic fever 3 demonstrated prolonged abnormal antistreptolysin titers. Four patients, including 1 with chronic glomerulonephritis, showed temporary increases, and 4 had no elevation of the titer (Table IV). The statistical differentiation of the earlier streptococcal infections into the allergic categories is shown in Table V.

DISCUSSION

Of the 160 patients studied, 41 or 25.6 per cent demonstrated antistreptolysin titers above 166 units per milliliter on one or more occasions. This percentage was twice as great as the 12.7 per cent reported by Rantz, Jacobs, and Kirby[20] in their study of the antistreptolysin in normal individuals, but this high incidence of abnormal titer may be expected in the region of the Great Lakes.[13, 22]

Thirty-two of the 41 patients (78 per cent) showed intermittent or occasional transient abnormal increases in the antistreptolysin. In general these transitory elevations bore no relation to the clinical allergic picture. This was well illustrated by the patients with seasonal rhinitis or asthma in whom the antistreptolysin titer was increased during the other months of the year without any provoking effect on the allergic disease. Whether temporary increases appearing during periods of acute exacerbation had any bearing on the hypersensitive state was difficult to decide. A closer correlation between clinical findings and laboratory studies will be required to evaluate their significance in these instances.

TABLE III. PROLONGED ANTISTREPTOLYSIN TITERS OF NINE PATIENTS WITH INFECTIOUS AND ATOPIC-INFECTIOUS BRONCHIAL ASTHMA

	INFECTIOUS				ATOPIC-INFECTIOUS				
MONTHS	E. K.	N. R.	C. C.	M. K.	R. M.	G. K.	L. M.	J. W.	M. T.
Initial	333	250	250	50	250	125	100	250	333
2	250	250		250				125	250
3				250					
4		250	500	333					
5	166	500		166					333
6		500	250						500
7			250	333	333		250		250
8		250	250	250	333		250		
9		250					500		250
10		125					250		
11		125					250		
12									
13	250								
14							50		
15								125	
16								100	
17	250								
18						250			
19	166							100	
20	166								
21	250								
22	250								
23	250				250			250	
24						250		250	
25	500					250			
26	250								
27	250								
28	250								
29								250	
30	250				250				
31									
32									
33									
34									
35									
36									

Although the elevation of the antistreptolysin titer in the majority of the 41 patients tended to be transitory, 9 individuals repeatedly demonstrated increased levels (Table III). Four of these patients belonged in the infectious and 5 in the atopic-infectious group. It is notable that the titer has continued to be elevated in all of these patients except 1 with whom contact has been lost. In 2 individuals this prolonged increase has continued over 2 years; in the others a high titer has persisted from 3 to 8 months. Accordingly, in the

group of 78 patients considered to have infectious asthma, 11.5 per cent were found to have a persistently elevated antistreptolysin titer (Table II). Swift, Derich, and Hitchcock[23] and Harkavy[19] reported that sensitizations to many different organisms develop so that 11.5 per cent attributable to sensitization with Group A hemolytic streptococcus actually represents a significant proportion of the numerous bacterial antigens.

There were 11 patients who gave histories of scarlet fever and/or rheumatic fever (Tables IV and V). Only 3 of these patients, all of whom belonged in the infectious or atopic-infectious asthma group, maintained elevated antistreptolysin titers. Two of these individuals had had scarlet fever and 1 had had rheumatic fever. A period of at least 3 years intervened in each instance between the earlier streptococcal disease and the demonstration of increased antistreptolysin in the present study. Mote and Jones[8] believed that the antistreptolysin index may remain elevated for months after the onset of rheumatic fever but that eventually it may fall to insignificant levels even when pronounced clinical manifestations persist. It seems improbable, therefore, that the antistreptolysin levels in these 3 patients could be directly attributable to the previous streptococcal infection even though it may have initiated the specific bacterial sensitization.

TABLE IV. INCIDENCE OF ABNORMAL ANTISTREPTOLYSIN TITERS IN PATIENTS WITH PRIOR RHEUMATIC AND/OR SCARLET FEVER

PRIOR STREPTOCOCCAL DISEASE	NUMBER OF PATIENTS	PROLONGED INCREASED TITER	TEMPORARY INCREASED TITER	NO INCREASE
Scarlet fever	6	2	2	2
Scarlet fever and rheumatic fever	3		1	2
Rheumatic fever	1	1		
Rheumatic fever and nephritis	1		1	

Since no standard criterion for persistence of increased antistreptolysin titers has been established, demonstration of 3 or more consecutive elevated titers over a period of 3 months was arbitrarily chosen. Rantz, Jacobs, and Kirby[20] reported that, after tonsillectomy, elevated antistreptolysin titers fell to normal within 60 days in 90 per cent of the cases. Accordingly, an elevated titer persisting for 3 months or more indicates the probable presence of chronic hemolytic streptococcal infection. Coburn and Pauli[24, 25] felt that a prolonged elevation of antistreptolysin titers denoted continuous liberation of streptococcal antigens from some nidus of infection. To verify this view they cited the work of McBroom, who persistently observed high antistreptolysin levels in animals in whom hemolytic streptococcal infection had been established by the agar focus technique. Swift, Derich, and Hitchcock[23] emphasized that a focus of infection was necessary for the ready induction of bacterial sensitization. Harkavy,[19] in his work on vascular allergy, presented 16 patients with bronchial asthma in whom the sinuses were considered the site of infection responsible for bacterial sensitization. A prolonged elevated antistreptolysin titer in a patient with infectious allergy may be assumed to indicate the presence of a focus of streptococcal infection with resultant sensitiza-

tion to the hemolytic strepococcus. A similar connotation is assumed when an elevated antistreptolysin titer is regarded as corroborative evidence in rheumatic fever.

The important role of the hemolytic streptococcus in the etiology of infectious asthma was clearly indicated in some of our cases. This was particularly true in one patient (M. K.) who had recurring exacerbations of asthma after repeated attacks of pharyngitis. An exacerbation of symptoms also occurred in this patient after an injection of bacterial vaccine. The antistreptolysin titer was found to be constantly elevated and hemolytic streptococci were recovered from throat cultures on several occasions. The correlation between bacterial infections in this patient and evidence of clinical and immunologic responses strongly suggested that the streptococcus or its products was directly responsible for the asthmatic attacks.

TABLE V. CLASSIFICATION OF PATIENTS WITH RHEUMATIC AND/OR SCARLET FEVER ACCORDING TO MANIFEST ALLERGIC DISEASE

PATIENT	AGE SEX	AL-LERGY	DURATION (YEARS)	S.F. R.F.	AGE	SPAN STREPTO-COCCAL DISEASE AND TITER (YEARS)	ABNORMAL ASL TITER	NUM-BER OF TITERS	NUM-BER IN-CREASED
1. A. C.	16M	A.R.	14	S.F.	9	7	No rise	3	
2. A. A.	40F	A.R.	10	S. F.	10	30	No rise	2	
3. M. L.	33F	A.R.	17	R.F., nephritis	20 23	11	Transitory	4	1
4. J. B.	45M	A.A.	3	S.F.	8	37	Transitory	3	1
5. D. L.	41F	A.R. A.A.	31	S.F.	7	34	Transitory	3	1
6. Z. R.	35F	A.R. A.A.	25	S.F. R.F.	7 9	25 23	No rise	4	
7. M. T.	20F	A.A. I.A.	14	S.F.	5	15	Prolonged	6	6
8. R. M.	21F	A.A. I.A.	9	S.F.	14	5	Prolonged	5	5
9. G. K.	8M	A.A. I.A.	2	R.F.	5	3	Prolonged	4	3
10. L. G.	33F	A.A. I.A.	9	S.F., chorea rheumatic heart disease	4 8	27 23	No rise	4	
11. E. F.	59F	I.A.	4	S.F. R.F.	9 25	48 32	Transitory	6	1

A.A., atopic asthma; A.R., atopic rhinitis; I.A., infectious asthma; R.F., rheumatic fever; S.F., scarlet fever.

The classification of bronchial asthma which we have used may not meet the approval of all. However, whether one accepts Rackemann's[26] classification of extrinsic and intrinsic asthma or Cooke's[27] division into noninfective and infective, there can be no disagreement that infection is frequently important in bronchial asthma. In spite of careful interpretation of clinical and laboratory evidence classification of asthmatic patients sometimes proves to be extremely difficult. Our classification of the 133 asthmatic patients (Table II) groups 45 or 33.8 per cent into the atopic division, 43 or 32.3 per cent into the infectious, 35 or 26.3 per cent into the atopic-infectious, and 10 or 7.5 per cent into the indeterminate. Cooke's[27] figures for the first 3 groups were 50, 35, and 15 per cent, respectively.

The diagnosis of bacterial allergy often can be made only on presumptive evidences. In bronchial asthma an infectious etiology may be inferred by the initiation, provocation, or aggravation of the asthmatic state with the development of respiratory infections, by the exacerbation observed after injections of catarrhal or autogenous vaccine, and possibly by improvement observed after vaccine therapy or eradication of infected foci. Cutaneous tests with bacterial vaccines are not reliable. A leucocytosis or a roentgenogram indicative of paranasal sinus disease may denote infection but the implication is not specific. A persistently elevated antistreptolysin index can be employed as a helpful corroborative procedure in determining the etiologic role of Group A hemolytic streptococci in patients with infectious allergy.

SUMMARY

1. Antistreptolysin determinations were made on sera from 160 patients with respiratory allergy.

2. Forty-one patients (25.6 per cent) had elevated antistreptolysin titers on one or more occasions.

3. No significance relevant to the allergic state could be attached to transitory antistreptolysin increases. However, the demonstration of repeated abnormal antistreptolysin titers in 9 asthmatic patients was considered significant.

4. These 9 patients comprised 11.5 per cent of 78 patients with infectious asthma. This figure bears great significance in the realization that sensitization to numerous other bacterial antigens can take place.

5. It did not seem probable that earlier streptococcal diseases (scarlet fever, rheumatic fever) had any direct influence on the antistreptolysin index of the present study.

6. Persistently elevated antistreptolysin titers apparently indicate the presence of a focus of hemolytic streptococcal infections. Since such a focus is capable of inducing bacterial sensitization, a persistently elevated antistreptolysin titer in patients with infectious asthma could imply that sensitization to Group A hemolytic streptococcus exists and is of clinical importance in the allergic state.

7. Continued critical study of the antistreptolysin titer in infectious allergy appears justified by the suggestive results of the survey.

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IMMUNOPHYSIOLOGY OF SERUM SICKNESS

Alterations in the Blood Volume and Thiocyanate Space in Relation to Humoral Antibodies in Rabbits Sensitized With Human Albumin or Globulin

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THE physiologic disturbances resulting from immune reactions which follow the introduction of closely related purified antigens have received scant attention. Many years ago disturbances in the distribution of body fluids were observed clinically and alterations in renal function were detected during the course of serum disease.[1-4] With the development of chemical methods for separation of serum into fairly homogeneous fractions of reasonable purity, it has been possible to approach the problem of experimental hypersensitivity to foreign proteins in animals more definitively.

The histological and serological sequences in rabbits sensitized with albumin and globulin fractions of bovine serum have been described.[5] The localization of protein antigens of various molecular sizes in the tissues of a heterologous animal by homologous antibody labeled with fluorescein has been reported.[6]

In a previous study it was found that rabbits sensitized by the intravenous injection of human plasma showed a decrease in the blood volume and an increase in the thiocyanate space which could be related to the time at which humoral antibody was first detected.[7] In preliminary studies with whole plasma, serial determinations of the fluid volumes detected two separate alterations in the space available for dilution of thiocyanate ion. These observations suggested that the two peaks were the result of physiologic defects attributable to reactions to two separate antigens from the plasma. These results were analogous to the appearance of anatomic lesions at different times following the injection of two separate serum fractions.[5]

Accordingly, the present experiments were conducted to study the changes in distribution of fluids induced by antigen-antibody reactions resulting from purified fractions of human serum of different molecular size.

MATERIALS AND METHODS

Twenty-nine domestic rabbits of mixed breeds, weighing roughly two kilograms each, were used. Animals were placed in individual cages and fed

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a stock diet* supplemented once weekly by fresh green vegetables. Water was given without restriction.

Crystalline Human Serum Albumin.†—The very limited quantity of crystalline human serum albumin available was dissolved in sterile physiologic saline solution (2 Gm. in 10 ml.). No preservative was added and the solution was injected immediately without other sterilization. This solution was further diluted to a final concentration of 1:1000 in physiologic saline for use as antigen in the precipitin tests.

Human Serum Albumin.†—Concentrated salt-poor human normal serum albumin (25 Gm. in 100 ml.) was injected undiluted. The material was diluted 1:100 in physiologic saline for use as antigen in the precipitin tests.

Human Serum Globulin.†—Human immune serum gamma globulin (12.3 Gm. in 100 ml.) was injected undiluted. The material was diluted 1:100 in physiologic saline for use as antigen in the precipitin tests.

Only one lot of each of the antigenic materials was used to complete all of the experiments.

Chemical Techniques.—The plasma volume was determined by the T-1824 (Evans Blue) dye method. Syringes holding 2 milliliters were calibrated to deliver 0.5 ml. of a solution containing 3 mg. of the dye per milliliter. Two different lots of dye were used for the albumin and globulin experiments. The thiocyanate space was determined simultaneously. Syringes holding 10 ml. were calibrated and 2.0 ml. of a solution containing 50 mg. of sodium thiocyanate per milliliter were injected.

The concentrations of the dye in rabbit serum were determined by the Evelyn photoelectric microcolorimeter and the thiocyanate concentrations with the Evelyn photoelectric macrocolorimeter.[7]

Hematocrit readings were made on oxalated blood placed in Wintrobe tubes, centrifuged at 3,000 revolutions per minute at a radius of 15 cm. for 30 minutes.

The total blood volume was calculated from the plasma volume and the hematocrit.

Immunologic Techniques.—Undiluted rabbit serum was placed in 2 by 20 mm. tubes to a height of 1 cm. and overlayed with 0.5 milliliter of the diluted antigen. The tubes were left at room temperature and the presence or absence of precipitation at the interface was detected by observation in reflected artificial light against a dark background after an interval of one hour. Each tube was compared with a control.

Skin tests were not done in order to avoid additional injections of antigen. The dye T-1824 has previously been shown not to induce precipitins or positive skin tests in rabbits.[7]

Experimental Procedure.—In the morning before feeding, an ear vein was nicked with a knife and 2 ml. of blood collected in a dry test tube and allowed to clot; 1 ml. was then collected in another dry tube containing 6 mg. of ammonium oxalate and 4 mg. of potassium oxalate. The dye was injected into a

*Kasco Complete Rabbit Ration, Kasco Mills, Incorporated, Toledo, Ohio.
†Furnished by the American Red Cross.

TABLE I. MEAN OF TWO BASELINE AND TWO RESPONSE VALUES IN RABBITS SENSITIZED BY THE INTRAVENOUS INJECTION OF 0.5 GM. PER KG. OF CONCENTRATED HUMAN ALBUMIN (GROUP 2)

	BASELINE					RESPONSE*					
RABBIT NUMBER	WEIGHT IN KILOGRAMS	THIOCYANATE SPACE ML./KG.	PLASMA VOLUME ML./KG.	TOTAL BLOOD VOLUME ML./KG.	HEMATOCRIT VOLS. %	PRECIPITIN POSITIVE DAY	WEIGHT IN KILOGRAMS	THIOCYANATE SPACE ML./KG.	PLASMA VOLUME ML./KG.	TOTAL BLOOD VOLUME ML./KG.	HEMATOCRIT VOLS. %
1	2.50	157.6	44.4	76.4	42.0	8	2.50	172.0	40.0	63.6	37.5
2	2.27	179.3	39.2	63.0	37.5	7	2.61	226.8	29.9	46.0	36.0
3	2.50	163.0	34.8	58.0	40.0	7	2.64	206.8	29.9	48.5	38.5
4	2.52	146.8	40.8	69.0	41.0	8	2.75	143.6	33.8	55.3	38.5
5	2.27	170.5	45.8	72.2	37.0	8	2.52	165.1	35.7	54.4	34.5
6	2.33	165.2	36.1	60.9	41.0	9	2.60	185.0	28.5	46.5	39.0
7	2.50	155.2	47.2	77.2	40.0	5	2.66	178.9	37.9	61.3	39.0
8	2.64	158.7	42.4	75.0	44.0	6	2.81	177.2	31.3	50.5	40.0
9	2.35	160.4	40.0	65.5	39.5	7	2.66	186.5	30.8	48.9	36.5
10	2.16	184.3	37.5	63.9	41.5	6	2.50	203.6	28.8	45.2	36.5
11	2.70	146.3	35.6	58.9	39.5	7	2.84	168.0	29.9	46.1	35.5
12	1.93	189.6	42.5	66.8	36.5	7	2.39	200.8	32.2	49.0	34.0
Mean	2.39	164.7	40.5	67.2	40.0	7.1	2.62	184.6	32.4	51.3	37.1

*The mean of two consecutive determinations at the start of the experiment is compared with the mean of two consecutive determinations in the same rabbit done on the day precipitins to concentrated human albumin appeared and on the next day.

vein in the opposite ear, the syringe changed, and the sodium thiocyanate injected through the same needle within one minute. Ten minutes following completion of the injection, 2 ml. of blood were collected from the first ear. When serial determinations were previously done, this arbitrary mixing time was found to give reproducible results for both blood volume and thiocyanate space.[8]

Preliminary Experiments.—In order to establish the minimal sensitizing dose, 3 rabbits were given a single subcutaneous injection in the interscapular region of 0.5 Gm. per kilogram of concentrated human albumin. Two rabbits developed positive precipitin tests on the twenty-ninth day, but the third animal was still negative on the thirty-second.

A single subcutaneous injection of 0.75 Gm. per kilogram of concentrated human albumin was then given four other rabbits. Two animals developed positive precipitin tests at 13 days and 2 at 14 days following injection.

Definitive Experiments.—Two baseline determinations were made on successive days on each of 5 rabbits (Group 1). After the second determination, each animal was injected subcutaneously with a single dose of 0.75 Gm. per kilogram of crystalline albumin. Precipitin tests were performed daily on each rabbit, but no further fluid volume determinations were done until the day that a positive precipitin reaction was first obtained. The measurements were repeated on that day and the following day.

Twelve rabbits (Group 2) were treated in the same fashion except that a single intravenous injection of concentrated albumin in a dose of 0.5 Gm. per kilogram was given.

Six rabbits (Group 3) were studied in an identical manner except that 0.25 Gm. per kilogram of serum globulin was given intravenously.

Statistical Analysis.—The total blood volume, plasma volume, hematocrit, thiocyanate space and weight were recorded in absolute values. The mean of the two baseline determinations on each animal was compared with the mean of the two response determinations made on the day that precipitins appeared and on the following day. The mean differences between the baseline and response values were calculated. The calculated value for "t" was compared with the value for n-1 degrees of freedom as obtained from standard tables. The value was considered significant if P was less than 0.01.

The data obtained in absolute values were then calculated in terms of milliliters per kilogram of body weight and the statistical significance was determined. Each animal served as its own control. No attempt was made to compare one experimental group with another.

RESULTS

General Observations.—Clinical serum sickness, manifested by erythema or edema, was not observed in any of the groups with the doses used.

Crystalline Human Serum Albumin (Group 1).—Positive precipitin tests appeared in all animals at a mean of 22.5 days. No significant changes were found in any of the response values when they were compared with the baseline values.

Human Serum Albumin (Group 2).—Positive precipitin tests developed in all animals at a mean of 7.1 days. The alterations in thiocyanate space, plasma volume, total blood volume, hematocrit and body weight are summarized in Table I, the statistical analyses in Table II.

TABLE II. STATISTICAL SIGNIFICANCE OF ALTERATIONS IN FLUID SPACES IN RABBITS SENSITIZED WITH CONCENTRATED HUMAN ALBUMIN

	WEIGHT IN KILOGRAMS	THIOCYANATE SPACE ML.	PLASMA VOLUME ML.	TOTAL BLOOD VOLUME ML.	HEMATOCRIT VOLS. %
$\bar{d}$	+ .230	+91.92	−11.40	−26.40	−2.83
$s_{\bar{d}}$	.035	13.50	1.44	3.12	.37
t	6.570	6.81	7.92	8.46	7.65
		ML./KG.*	ML./KG.*	ML./KG.*	
$\bar{d}$		+19.82	−8.08	−16.04	
$s_{\bar{d}}$		4.50	.20	1.10	
t		4.40	40.40	14.58	

*Calculated in terms of weight on the day of determination.

$\bar{d}$ = mean difference

$s_{\bar{d}}$ = standard error of the mean difference

S = summation of, n = number of animals.

$$t = \frac{\bar{d}}{s_{\bar{d}}} \qquad s_{\bar{d}} = \sqrt{\frac{Sd^2 - \frac{(Sd)^2}{n}}{n(n-1)}}$$

For 11 degrees of freedom $t = 3.106$; $P = <.01$

The data all show statistically significant differences between the baseline values and those obtained at the time of the humoral antibody response.

A significant increase in the mean thiocyanate space was noted at the time the humoral antibody was first detected. A significant increase in body weight occurred during the period of alteration in thiocyanate space. In contrast to the increase in thiocyanate space and weight, significant decreases in plasma volume, total blood volume, and hematocrit occurred in all animals.

All the data are statistically significant whether the calculations are based on the comparison of absolute values or of values based on milliliters per kilogram of body weight.

Human Serum Globulin (Group 3).—All animals developed positive precipitin tests at a mean of 9.0 days. The alterations in thiocyanate space, plasma volume, total blood volume, hematocrit and body weight are summarized in Table III, the statistical analyses in Table IV.

The increase in thiocyanate space was significant only when the data were analyzed in absolute values. The increase in body weight was significant. The decreases in plasma volume, total blood volume and hematocrit were significant whether the data were calculated in absolute values or in terms of milliliters per kilogram of weight.

DISCUSSION

The observations reported demonstrate that immune reactions to albumin and globulin fractions of human serum are associated with alterations in distribution of fluids within the body. The changes were detected earlier and were quantitatively greater after the injection of albumin than after globulin, but qualitatively they were the same. The absence of clinical manifestations of serum disease in our animals suggests that the disease was mild. The variation in the time of appearance of precipitins in relation to the experiments of others

TABLE III. MEAN OF TWO BASELINE AND TWO RESPONSE VALUES IN RABBITS SENSITIZED BY THE INTRAVENOUS INJECTION OF 0.25 GM. PER KG. OF HUMAN GAMMA GLOBULIN (GROUP 3)

	BASELINE					RESPONSE*					
RABBIT NUMBER	WEIGHT IN KILOGRAMS	THIOCYANATE SPACE ML./KG.	PLASMA VOLUME ML./KG.	TOTAL BLOOD VOLUME ML./KG.	HEMATOCRIT VOLS. %	PRECIPITIN POSITIVE DAY	WEIGHT IN KILOGRAMS	THIOCYANATE SPACE ML./KG.	PLASMA VOLUME ML./KG.	TOTAL BLOOD VOLUME ML./KG.	HEMATOCRIT VOLS. %
13	1.96	250.0	56.1	93.4	39.0	9	2.10	261.9	46.2	74.3	36.5
14	2.09	234.0	58.4	101.0	41.0	7	2.33	215.5	46.4	79.8	39.5
15	1.91	266.0	67.5	103.1	35.0	9	1.93	302.6	57.0	85.0	33.5
16	1.56	313.5	69.2	112.8	36.5	10	1.70	329.4	52.9	89.4	34.5
17	1.93	273.6	64.8	106.2	39.0	8	2.05	275.6	55.1	81.5	34.0
18	2.10	262.8	70.0	103.8	42.0	11	2.18	278.8	56.0	79.4	39.0
Mean	1.93	233.3	64.3	103.4	38.8	9.0	2.05	277.3	52.3	81.6	36.2

*The mean of two consecutive determinations at the start of the experiment is compared with the mean of two consecutive determinations in the same rabbit done on the day precipitins to human gamma globulin appeared and on the next day.

TABLE IV. STATISTICAL SIGNIFICANCE OF ALTERATIONS IN FLUID SPACES IN RABBITS SENSITIZED WITH HUMAN GAMMA GLOBULIN

	WEIGHT IN KILOGRAMS	THIOCYANATE SPACE ML.	PLASMA VOLUME ML.	TOTAL BLOOD VOLUME ML.	HEMATOCRIT VOLS. %
$\bar{d}$	+0.122	+52.20	−16.80	−32.00	−2.58
$s_{\bar{d}}$	0.028	9.60	1.99	3.40	0.54
t	4.370	5.43	8.44	9.40	4.78
		ML./KG.*	ML./KG.*	ML./KG.*	
$\bar{d}$		+10.70	−12.23	−21.80	
$s_{\bar{d}}$		7.40	1.37	1.14	
t		1.45	8.93	19.10	

*Calculated in terms of weight on the day of determination.
For 5 degrees of freedom, t = 4.032; P = <.01.
With the exception of the thiocyanate space in ml. per kg. the data all show statistically significant differences between the baseline values and those obtained at the time of the humoral antibody response.

may be due to differences in the species of serum utilized as antigen. Other investigators have used chiefly horse or bovine serum.[4, 5, 9] The preliminary experiments indicate that the size of the dose affects the incubation period, but not the severity of the disease.

The crystalline serum albumin used may well have been antigenically altered in the process of crystallization. The appreciably longer period before precipitin tests became positive, as compared with concentrated serum albumin, is suggestive of impaired antigenicity. Another factor contributing to the longer incubation period may have been the difference in the route of administration of the antigen. The fact that significant physiologic alterations were not detected may be due to either of these factors, or to both.

The increase in space available for dilution of the thiocyanate ion at the time circulating humoral antibodies appeared, when compared with the control period in the same animal, indicates that this small molecule diffused into some extravascular space to a greater extent. The loss of water and ions from the vascular tree into tissues would readily explain the observations of retention by the body of water, salt and chlorides during serum disease and pneumonia.[2, 10] The decrease in circulating blood volume confirms the suggestion that particles had left the circulation.[7] The colloids lost to the interstitial spaces would tend to retain water extravascularly until they had been reabsorbed or broken down in the tissues. It is well known that in severe immune reactions of the anaphylactoid type hemorrhages, due to the extravasation of the even larger red blood cell, appear in various organs.

The observations can be interpreted as indicating an increase in permeability of the vascular tree, so that crystalloids, colloids, and red blood cells are progressively lost from the circulation as the magnitude of the defect increases with increase in the clinical severity of the disease. The alterations in the vascular tree can be visualized as a series of pores, probably in the capillary wall where the normal extravascular circulation of crystalloids, and to a lesser extent small protein molecules such as albumin, is known to occur. In mild instances of serum disease water and ions which normally traverse the membranes would

leave the blood more readily. Larger molecules such as protein would be lost in more severe instances and red blood cells would pass out of the vascular tree only in the most severe reactions.

A uniform, significant reduction in the hematocrit occurred in all animals in Groups 2 and 3. Since the plasma volume had decreased, the total circulating red cell mass must have decreased also. There was no clinical evidence of increased capillary permeability to red cells as evidenced by hemorrhage or petechiae. The clinical disease induced appeared to be too mild to account for the decrease in hematocrit on the basis of extravasation of red cells out of the vascular tree. The possibility of hemolysis must be considered; jaundice has been previously observed in another group of animals sensitized with human plasma. No such sign was detected in the present study. It is also possible that a shunting and pooling of red cells in some inactive tissue or organs had occurred. No adequate explanation can be given at the present time for this reduction in hematocrit.

The proportionately smaller increase in thiocyanate space in the animals injected with globulin, as compared with those injected with albumin, may have been due to the fact that the antigenic stimulus was quantitatively less. A smaller dose was administered and the larger size of the molecule would mean that fewer antigenic particles were injected in a given weight of serum. Furthermore, the globulin molecules may be less antigenic than the smaller albumin molecules. The reduction in the incidence of clinical serum disease noted since the introduction of therapeutic antisera composed chiefly of the gamma globulin fraction lends further support to this hypothesis. The cells to which antigens of various size attach, as well as the speed of attachment, vary with the type of antigen injected.[6] The globulin molecule may attach to cells which have less capacity for the production of antibodies.

The increase in extravascular fluid space as measured by the thiocyanate ion could not always be correlated with an increase in weight. The alterations cannot therefore be attributed solely to a defect in capillary permeability with retention of extra fluid in the interstitial spaces. Apparently the normal distribution of fluid in the body was altered, probably as the result of an increase in permeability of cellular membranes as well. It is not known whether the thiocyanate ion normally diffuses into cells or not. In any event these observations indicate that at the time humoral antibodies were detected the permeability of membranes to these ions was increased, so that they diffused from blood into interstitial spaces and probably from interstitial fluid spaces into cells.

Histological techniques have demonstrated that after the injection of antigens cellular reactions can be detected by anatomic methods before humoral antibodies are present.[5, 9] It has been presumed that these histological changes are the result of antigen-antibody reactions taking place on the cell membrane or within the cell, but the speed with which specific antibodies are formed within cells or attached to them is not known.

The role of antigen-antibody reactions in the production of anatomic glomerular lesions following the injection of bovine globulin into rabbits has

recently been questioned.[9] The fact that anatomic lesions appear before humoral immunity is detectable suggests the alternative possibility that physiochemical relationships concerned with the hydration of intraglomerular proteins may effect changes without an immune reaction taking place.

Correlation of these physiologic experiments with previous histologic studies could not always be made. The injection of albumin fractions of bovine or horse serum results in generalized arterial lesions; the globulin fractions produce glomerular lesions more frequently.[5, 9] It is likely that the physiologic defect which we have studied occurs not in the artery, but in the capillary for reasons given earlier. The physiologic defect reaches its maximum after the anatomic lesion appears, is completely reversible if the animal lives, and disappears at a time when the anatomic lesion may persist.[5, 7] In rickettsial diseases reversible physiologic changes may be present which are out of all proportion in magnitude to the number of anatomic vascular lesions present.[11] The similarity of the histological picture in rickettsial diseases and serum sickness suggest that some common denominator may be present. An immune reaction is such a factor.

SUMMARY

1. Alterations in the distribution of fluids associated with the development of humoral immunity were detected in rabbits injected intravenously with human serum albumin or globulin.

2. Increase in the space available for dilution of thiocyanate ions and decreases in plasma volume, total blood volume and hematocrit occurred at the time circulating antibody (precipitins) appeared.

3. The changes appeared earlier (at a mean of 7.1 days) following the injection of albumin than after the injection of globulin (9.0 days). Crystalline human serum albumin, injected subcutaneously, did not produce significant physiologic disturbances and the appearance of precipitins was delayed for a mean of 22.5 days. These findings were interpreted as indicating an alteration in antigenicity of the protein in the process of crystallization, but may have been related to the subcutaneous route of injection.

4. The redistribution of fluid was interpreted as indicating a defect in permeability of capillaries and of cell walls as a result of antigen-antibody reactions.

5. The correlation with anatomic findings by histologic techniques is discussed.

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TOPICAL APPLICATION OF CORTISONE IN INTRACTABLE BRONCHIAL ASTHMA

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CORTISONE has acquired wide acceptance as an adjunct in the treatment of status asthmaticus and intractable bronchial asthma. According to present accepted methods of administration and dosage, its effects are usually short lived, and if treatment is prolonged one must guard against harmful side effects. It is not within the scope of this paper to discuss the variety or severity of these side reactions. However, we wish to point out that if small dosage could be employed effectively by some other approach, little or no such hazard would be involved.

Bordley and collaborators[1] noted that the topical application of cortisone caused regression of allergic edema of the mucosa of the nose and paranasal sinuses. Functional air space was increased and mucous polyps, when present, regressed in size. This phenomenon had previously been described by Rose, Pare, Pump, and Stanford[2] with intra-muscular cortisone. Steffenson and collaborators[3] have shown that the topical application of cortisone caused resolution of exudates in the cornea of the eye. In both instances of topical application, relatively minute amounts of cortisone were employed.

From the work of these investigators, it appears that the topical application of cortisone exerts a local tissue effect resulting in regression of the edematous mucous membrane. Dyspnea in bronchial asthma is due in great part to an edema of the bronchial mucous membrane. Regression of this edema should have a salutary effect in bronchial asthma, by removing a major impediment to free respiration. It was our purpose to determine whether and to what degree these premises proved correct.

TECHNIQUE

Cortisone was applied topically to the bronchial mucosa using the following technique:

Cannula Technique.—The patient was premedicated with 0.05 Gm. Seconal. Anesthesia of the pharynx, larynx, and trachea was obtained with topical application of 1 per cent pontocaine. Twenty-five mg. of Cortisone mixed with 2.5 ml. of water were instilled into the trachea with a Luken's cannula.

Bronchoscopic Technique.—The patient was premedicated with 0.1 Gm. of Sodium Pentobarbital and 0.4 mg. of atropin sulfate. Ten per cent Cocaine in 1:1000 epinephrine solution was applied topically to anesthetize the pharynx and larynx. Four milliliters of 4 per cent cocaine in saline were instilled intratracheally. The bronchoscope was inserted, through which 50 mg. of cortisone in 8 ml. of saline was administered; half the solution being instilled directly into each main stem bronchus. Vital capacities were determined daily before, and for a few days after, therapy.

From St. Luke's Hospital, Cleveland, Ohio.

CASE REPORTS

CASE 1. M. W., a 53-year-old white housewife, was first seen Feb. 21, 1951, in severe asthma. The patient had been in good health until 10 years previously. At that time she began to suffer from perennial rhinitis with occasional attacks of asthma. Her symptoms were aggravated during the winter months. She was under allergic management for six years. Her paranasal sinuses were repeatedly irrigated and nasal polypectomies were performed on several occasions. One month previously, wheezing and dyspnea became continuous, being relieved for hourly periods by injections of epinephrin. Significant features of the physical examination were dyspnea and moist rales throughout the chest. The heart findings were normal, the blood pressure, 116/72. The results of the usual laboratory tests were within the normal limits. Skin tests, both scratch and intradermal, were negative. The x-ray report showed no evidence of active pulmonary disease; the heart normal; there was aortic arteriosclerosis. Paranasal sinus x-rays showed increased density of the ethmoids.

On Feb. 26, 1951, 25 mg. of cortisone was instilled by cannula intratracheally. Within 24 hours, dyspnea ceased and the chest was free of adventitious sounds. She remained symptom-free for approximately two weeks, when symptoms gradually recurred. For two weeks thereafter she suffered severe asthma accompanied by cough which was difficult to control. On April 4th and April 6th, 1951, 50 mg. of cortisone was instilled via bronchoscope. Within two days, the chest was clear of all adventitious sounds and the asthma had entirely abated. Her condition was such as to permit a Marshall-Marchetti operation for bladder incontinence on April 10, 1951. She remained symptom-free until the first week of August, 1951. For two weeks thereafter, she complained of intractable coughing. This was followed by daily asthmatic seizures until the present time (Aug. 24, 1951).

CASE 2. M. R. is a 49-year-old housewife. The patient complained of a racking cough and perennial bronchial asthma for 15 years. Her symptoms had been almost constant for the past 6 months. The physical examination revealed wheezes throughout both lungs. The heart was normal, the blood pressure, 120/80. X-ray examination of chest revealed normal findings and the bronchogram was also normal. Urinalysis was negative; the blood count: R.B.C. 5,290,000, Hgb. 16.6 Gm., W.B.C. 9500. Skin tests were positive to house dust, ragweed, feathers, rabbit hair, cat hair, tobacco and alternaria. There were various positive food tests which could not be correlated with symptoms. She has been treated with injections of ragweed, house dust, and alternaria extracts. Under allergic management, symptoms were improved but she was never free of some degree of respiratory embarrassment.

On each of March 5, 6, and 8, 1951, 25 mg. of cortisone was instilled by cannula. Her cough increased, becoming more productive for a few days. Thereafter, wheezing and dyspnea disappeared. She estimated that she was 90 per cent improved. This continued until March 24, 1951. Symptoms then returned and were becoming progressively worse. On April 2 and again on April 4, 1951, 50 mg. of cortisone was administered via bronchoscope. For the following two months the patient had been entirely asymptomatic when asthma gradually reappeared. This case provided us with an opportunity to determine the effect of intratracheally-instilled Cocaine. 4 ml. of 4 per cent Cocaine were thus administered. This afforded her no relief.

CASE 3. F. S. is a 40-year-old white male truck driver, who has had bronchial asthma since childhood. He noted that house dust caused his asthma. He suffered acute severe episodes, lasting 3 to 4 days, about twice a month. Between these episodes he had a chronic cough with impairment of respiration noted as dyspnea on more than average exertion. About March, 1950, his attacks increased in frequency and severity requiring hospitalization and frequent absences from work. The physical examination revealed wheezes throughout the chest. The heart findings were normal, the blood pressure, 110/70. X-ray of the chest revealed emphysema. There were large positive skin tests to grass pollen, ragweed pollen, and house dust. The patient was advised as to house dust precautions and treated with injections of grass, and ragweed pollens, and dust extracts. His condition improved somewhat but it was felt that this, for the most part, was due to symptomatic therapy. His chest was never free of wheezes and prolonged expiration.

On March 2, 3, 5, and 6, 1951, 25 mg. of cortisone was introduced by canula. Symptomatic improvement began March 7, 1951, coincident with an increased productive cough. The patient explained his relief in the words, "the phlegm comes up by itself" and, "can breathe with hardly any effort." Thereafter, even though physical examination revealed an occasional wheeze, he enjoyed uninterrupted sleep, his breathing was relatively effortless, and he was able to do more work with less fatigue. After about 3 weeks, symptoms returned to about twenty-five per cent of their former level as judged subjectively and by the amount of antiasthmatic medication employed. Physical examination on May 29, 1951, revealed an occasional wheeze in either chest. He was not seen again until August, 1951, when symptoms again equaled his pretreatment level.

CASE 4. M. B. is a 37-year-old housewife whose asthmatic attacks began in September, 1931 and continued throughout that month. Her attacks were intermittent thereafter until the following ragweed pollen season, when they continued throughout that period. This pattern was followed until August of 1947 when she was hospitalized for status asthmaticus. In addition to clinical sensitivity to ragweed pollen, the patient noted symptoms on inhalation of house dust and ingestion of cauliflower, grapes, and pork.

She was placed on dust-free precautions; positive test foods were eliminated from the diet and treatment for ragweed pollen, dust and alternaria was instituted. On two occasions, constitutional reactions were produced by house dust injections. In addition, symptomatic treatment with potassium iodide, ephedrine, inhalation of Norisodrene crystals or 1:100 epinephrine, rectal aminophyllin and self-injected 1:1000 epinephrine was employed. At no time during the past three years was she free from some degree of asthma and averaged four hospitalizations a year for status asthmaticus. Significant physical findings were obvious dyspnea, increased expiration time and dry rales throughout the chest. The heart findings were normal, blood pressure, 120/76. The laboratory findings were: W.B.C. 8500, the differential count showing 6 eosinophiles, Hgb. 15.2 gm., and R.B.C. 5,120,000. The urinalysis showed no abnormal findings. The x-ray showed no cardiac enlargement. There was generalized emphysema. Skin tests were positive for house dust, feathers, hog hair, horse hair, alternaria, and several foods.

Twenty-five milligrams of cortisone was instilled intratracheally by cannula on each of March 5, 6, and 8, 1951. This was followed by considerable productive cough lasting several days. On March 12, 1951, definite improvement was noted. On March 13 and 14, 1951, she was free from dyspnea or auscultatory wheezing for the first time in the past three years. During the subsequent two weeks she estimated 75 per cent improvement. This was borne out by proportionate decrease of antiasthmatic medication as compared to that previously used. She enjoyed uninterrupted sleep and was now able to carry on her household duties with comparative ease. She gradually reverted to her original state and on April 16 and 18, 1951, 50 mg. of cortisone was administered via bronchoscope. The vital capacity readings were as follows: 4-16-51, 2300 ml.; 4-17-51, 2500 ml.; 4-18-51, 3000 ml. After the instillations she was entirely free from asthma. Her chest was clear to auscultation. After two days, severe asthma returned.

CASE 5. S. S. is a 35-year-old-housewife who was first seen March 9, 1951. Her first attack of asthma occurred in the spring of 1936. Six years ago she was treated with house dust extract. While under such treatment for a period of four years, her symptoms were ameliorated. Two years ago, asthma became severe. Even when relatively free from dyspnea, wheezing was constant. She has noted asthma from contact with dog hair, fresh wool, insecticide and house dust. Physical examination revealed an emphysematous chest with wheezes throughout. The heart was normal, blood pressure 140/90. Laboratory findings: urinalysis negative, W.B.C. 8000, Hgb. 15.1. X-ray revealed generalized pulmonary emphysema. There were numerous positive tests to a variety of pollens, foods, and miscellaneous substances. Intradermal test with 1-40,000 Endo dust produced a wheal 2.5 cm. in diameter.

On April 23 and April 25, 1951, 50 mg. of cortisone was instilled via bronchoscope. This was followed by increased productive cough for a few days. Vital capacity readings were as follows: 4-23-51, 2000 ml.; 4-24-51, 2000 ml.; 4-25-51, 2200 ml.; 4-26-51, 2600 ml. After the instillations, she noted easier breathing and was able to do more work with less fatigue. She slept through the night, whereas previously she had to get up two or three times because of coughing and asthma. She estimates that she was 75 per cent improved for a period of two weeks. Her symptoms are increasing but are not as severe as before treatment.

CASE 6. C. G., a 45-year-old Negro housewife, has suffered from asthma since the age of 8 years. Symptoms are worse during fall season and through the winter months. She has had constant dyspnea for the past eight months. On physical examination, the patient exhibited dyspnea and wheezes throughout the chest. The heart was negative, blood pressure, 106/72. Laboratory findings: W.B.C. 5600, Hgb. 16.1, urinalysis negative. Skin tests were positive to dust, feathers, wool, cow hair, flaxseed, dog hair, horse hair, ragweed, chocolate, and pork. X-ray reported pleural density lower left lung field, fibrous changes in apices, prominent bronchovascular markings, heart not remarkable.

Fifty milligrams of cortisone was instilled via bronchoscope on each of March 6 and 8, 1951. The cough became more productive, breathing less labored, and wheezing decreased. She used less antiasthmatic medication, and estimated an improvement of 50 per cent for about two weeks. During the following four weeks, her symptoms became progressively more severe. On April 23 and April 25, 1951, 50 mg. of cortisone was gain instilled via bronchoscope. Vital capacity readings were as follows: 4-23-51, 1100 ml.; 4-24-51, 1400 ml.; 4-25-51, 1300 ml.; 4-26-51, 1200 ml. Following this, the patient again noted 50 per cent decrease in severity of asthma. She was able to do her housework without undue fatigue, and could sleep through the night without cough or dyspnea. After 10 days, she reverted to her original condition.

CASE 7. J. B. is a 52-year-old white, male bus driver, who first noticed fall hay fever and asthma in 1927. His symptoms were seasonal except that the inhalation of unusual amounts of house dust would cause asthma. One of us (M. L.) treated him in 1937 with ragweed and dust extracts. After one year of treatment he was entirely free of symptoms until the fall of 1945. At that time he was hospitalized for status asthmaticus. He was again symptom-free until the fall of 1946 when he again suffered status asthmaticus. Thenceforward, his dyspnea became continous and at no time during the past four years was his chest free of wheezing. He was treated with house dust, ragweed pollen, grass pollen and alternaria extracts. He used some form of symptomatic therapy every day. The physical examination revealed no cardiac abnormalities, blood pressure 110/60. The lungs revealed expiratory wheezes throughout. The laboratory findings were: W.B.C. 5100, Hgb. 14.8 gm.; urine findings within normal limits. X-ray revealed streaky horizontal shadows of increased density at the left base interpreted as segmental areas of atelectasis or remote zones of pulmonary fibrosis. The heart showed no enlargement. There was evidence of aortic arteriosclerosis.

On March 26 and again on March 28, 1951, 50 mg. of Cortisone was instilled via bronchoscope. On March 30, 1951, his chest was clear of wheezes for the first time since under our care. For the past 5 months he has noted only an occasional wheeze and has taken practically no medication. He states that he is 90 per cent improved.

CASE 8. Mrs. S. D., aged 63, first noted asthma in July, 1935. Her symptoms were worse during the winter season. Asthma increased in severity from year to year. When seen on Oct. 15, 1946, the patient averaged 6 to 10 injections of adrenalin daily. She weighed 108 pounds. Physical examination showed obvious dyspnea, emphysema, and wheezes throughout both chests; the x-ray revealed moderately heavy lung markings and emphysema; the heart was normal; the ethmoids showed a definite increase in density; the mucous membranes of the antra were thickened; and usual laboratory findings were within the limits of normal.

All varieties of symptomatic therapy were employed. At various times penicillin was administered intramuscularly and by aerosolization. Autogenous vaccine and nonspecific vaccine were injected. Her condition improved so, that one year later, although her symptoms were more or less constant, she weighed 129 lbs. During September of 1950, when her asthma

was particularly severe she received intramuscular cortisone for a period of three days. Considerable improvement resulted which lasted for two weeks. On June 9, 1951, 100 mg. of oral cortisone was given daily in divided doses for one week. This again resulted in improvement which lasted for 10 days. On July 12, 1951, 4 per cent Cocaine was instilled into the trachea via the bronchoscope. This resulted in an intensification of asthmatic symptoms so that she used 16 injections of adrenalin in the next 24 hours. During the following three weeks she averaged about 10 injections of adrenalin daily. On each of Aug. 3 and Aug. 6, 1951, 50 mg. of cortisone was instilled via bronchoscope. Vital capacity readings were as follows: 8-3-51, 1900 ml.; 8-4-51, 2000 ml.; 8-5-51, 2300 ml. She now noted freedom from dyspnea throughout the day, her cough disappeared, she no longer complained of fatigue and in general noted a sense of well-being. Nevertheless, she administered adrenalin two to three times during the night for incipient asthmatic symptoms. In her opinion, she was 90 per cent improved for three weeks. Thereafter, symptoms gradually increased in severity.

DISCUSSION

In the average asthmatic patient, dyspneic attacks are cyclic and intermittent. This makes evaluation of the effect of any new therapeutic modality difficult. Therefore, only those cases who had responded poorly or not at all to accepted allergic management, were selected for experiment. These cases suffered from chronic and relatively continuous respiratory disability, cough, fatigue and interrupted sleep. Even when free from dyspnea, wheezes were heard on auscultation.

From the protocols, it is evident that some measure of relief from asthma was afforded in every case by the topical application of cortisone to the bronchial mucosa. The degree of relief as reported, and noted by us objectively, followed one of three patterns: (1) Complete relief lasting for two months in Case 2 (Mrs. M. R.) and four months in Case 1 (Mrs. M. W.) (2) Partial relief (50-90 per cent) lasting two weeks to several months with gradual increase of symptoms as in Cases 3, 5, 6, 7 and 8. (3) Negligible relief as illustrated by Case 4 (Mrs. M. B.) who experienced complete relief for two days followed by virulent asthma. On a previous occasion she had been relatively free from symptoms for three weeks following instillation of cortisone.

Antiasthmatic medication was either discontinued or employed in very small amounts when compared to such medication previous to cortisone therapy. The patients remarked on their sense of freedom in breathing, lessened fatigue and enjoyment of sleep uninterrupted by cough or dyspnea. Adventitious chest sounds disappeared for varying lengths of time in the majority, however, the improvement was no less definite in the others even though adventitious sounds were in evidence.

Since low dosage of cortisone such as used here, when used orally or intramuscularly is ineffective in bronchial asthma, we infer that our results were brought about by local action at the tissue level. This is in consonance with effects noted by other investigators who employed cortisone topically in other conditions on other tissues.

Wet eosinophile counts were done. In three cases the counts exceeded normal limits. With therapy, the counts were increased in some and decreased in others. Since no deductions from these figures could be made, our report is not encumbered with the details.

As is evident, the vital capacities, where done, showed only a slight increase. It must be remembered these patients were chronic asthmatics with more or less permanent lung changes. Also, the figures do not reflect an abrupt change in a specific asthmatic attack. Therefore, the demonstration of only slight change in vital capacity does not militate against clinical relief from the asthmatic state.

One cannot ascribe the relief obtained to the use of 4 ml. Cocaine of 4 per cent Cocaine was instilled into the trachea of Cases 2 (Mrs. M. R.) and 8 (Mrs. S. D.) as controls. In each instance, the severity of the asthmatic attack was increased.

We hold no brief for the dosage, frequency or the manner of topical application of cortisone. Different dosage or more frequent treatment may prove more effective. The technique was changed from the use of the cannula to that of the bronchoscope because it was thought that a better and deeper distribution of cortisone would prove more effective. However, the relief afforded in Cases 1, 2, 3 and 4 by the cannula method demonstrates the effectiveness and practicability of this office procedure. Whether the instillation of cortisone in the office at regular intervals will keep these heretofore intractable asthmatics relatively free from symptoms remains to be seen.

CONCLUSIONS

1. Cortisone in small dosage was applied topically to the bronchial mucosa via cannula or bronchoscope to eight patients suffering from intractable bronchial asthma.

2. This procedure was followed by 50 to 100 per cent symptomatic relief for periods averaging two weeks to four months.

3. It would appear that cortisone has a local effect at the tissue level.

4. An optimum dosage and an optimum frequency of application is to be sought.

We wish to express our thanks to Drs. Don D. Brannan and H. F. Inderlied for the x-ray readings in this study.

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THE EFFECT OF THE MIAMI (FLA.) CLIMATE ON IMPORTED ALLERGIC PROBLEMS*

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IT IS generally accepted by workers in the field of allergy that weather conditions have a definite effect upon most allergic individuals.[1-5] The suggested corollary is that climatotherapy should be of real value. It is the purpose of this paper to evaluate the effect of the climate in the Miami, Florida, area upon one hundred fifty known allergic individuals who moved or had prolonged visits in this section of the country. These patients were consecutively chosen omitting only those whose symptoms first appeared in Florida. This community is ideal for such a study since during the past ten years there has been a great influx of population from all parts of the country.

For the purpose of clarification in describing the results of residence in Miami on the patients in this study, an attempt will be made to divide the total number into etiological groups. This approach will also reveal a superficial cross-section view of the known allergic problems in the Miami area. Certain criteria will evolve which should prove useful for those seeking benefit from climatotherapy in Miami.

INHALANT ALLERGY

Ragweed Allergy.—Climatotherapy in the sense of avoiding exposure to a known atmospheric allergen is, of course, reasonable if not excellent therapy. A patient who is sensitive to ragweed may come to Miami Beach during August and September and almost certainly find relief.[6, 7] The ragweed season in the Miami area extends from late June through October but, on Miami Beach, the highest count obtained in any twenty-four hour period was eight grains per sq. cm.[9] Counts in certain sections of Miami have, on occasion, been slightly higher.[7]

The basic requirement for obtaining symptomatic relief is that these patients be sensitive only to ragweed or that their other sensitivities be of little importance. There are, however, exceptions to the rule. Those patients classified as "AA," or the exquisitely sensitive type may have symptoms if, either by choice or necessity, they travel inland from Miami Beach to an area where ragweed is abundant and contact with a ragweed field is direct. The botanical explanation is that in this soil and climate ragweed (and perhaps other allergenic weeds, grasses and trees) is changing its characteristics to an insect pollinating plant with the production of large amounts of pollen, little of which is wind-borne.[10] Four such cases were found in this series, an example of which follows.

Case No. 866 (F. S.) A twenty-six-year-old man had hay fever in New York City during August and September from 1939 to 1945. He arrived in Miami in October, 1945, and was

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well until 1947 when his symptoms were present from July to September. He had no treatment that year. In 1948 his symptoms occurred from April to September. His home and office were on Miami Beach but since he was an accountant he soon visited all adjacent cities where he had most of his trouble. The prolongation of his 1948 season was found to be due to live oak sensitivity. Combined treatment with these allergens gave him complete relief during the past four years.

This case also illustrates a frequent observation in patients who lose "allergic balance." Coincident with the recurrence of ragweed pollinosis he, for the first time, developed a tree pollen sensitivity.

One additional problem worthy of consideration concerns a rather large group of sixteen patients who were sensitive to ragweed and came to Miami Beach to avoid this pollen but completely neglected allergic hygiene and dietary control necessary at home. It must be explained to a patient that simply by avoiding exposure to a major allergen he does not avoid the consequences of exposure to minor allergens, although this may occasionally appear to happen.

Tree Pollen Allergy.—Patients with respiratory allergy whose sensitivities are limited to the pollen group generally do well in the Miami area where the prevailing breeze comes from the ocean more than 80 per cent of the year. Furthermore these pollens are small in concentration and come from a large number of botanical structures, both known and unknown, which fortunately produce little pollen over long pollinating seasons and possess low antigenicity.[10] Often they require no treatment, but when necessary, smaller dosage with less frequent administration is adequate.

The exception to this rule consists of patients who, uncommonly, develop a sensitivity to our local trees. The long tree season in this area, somewhat variable each year, from December to April, as opposed to the short seasons in the north, indicates the need for treatment. The trees of importance are live oak and Australian pine.[8] The palms, Spanish moss, Malaleuca, and others are very doubtful factors but additional investigation is needed. There were seven such cases in this series.

Case No. 443 (M. Z.) A forty-nine-year-old man had a history of asthma and hay fever in New York City from 1931 to 1934. He was found sensitive to plantain, ragweed, grasses, and trees and received effectual treatment. He moved to Miami Beach in 1935, discontinued treatment, and remained well until 1940 when seasonal rhinitis and asthma developed from January to April. He was found sensitive to both Australian pine and live oak and specific treatment since 1945 has produced excellent results.

Grass Pollen Allergy.—Bermuda and Johnson grass represent the important known grass pollen allergens in this area with Napier, molasses, Natal, and other grasses still under observation.[7] The grass season extends from February through November with very low counts prevailing. Both Bermuda and Johnson are specific sensitizers but apparently less antigenic in this area than in other parts of the south and than northern grasses in their locale. We find no consistent skin-test evidence of a common antigen in Bermuda, Johnson, and northern grasses. We have also seen patients who give positive reactions to one or the other of our grasses. However, patients who have a history of multiple

and exquisite grass pollen sensitivity in the north are more likely to develop clinical allergy to grasses in this area. There were nine cases of grass pollen sensitivity in this series.

Case No. 1017 (E. G.) A twenty-eight-year-old man had typical symptoms of pollinosis in Baltimore, always during May and June, with onset at twelve years of age. During some years he also had symptoms in August and September. He was completely well during the war years in both Europe and the Pacific while on sea duty with the Navy. He came to Hollywood, Florida, in 1946 and was completely well until March 1948. Investigation revealed the already suspected sensitivity to orchard, timothy, red top and June grasses which are not found in this area, as well as Bermuda and Johnson grasses, which are prevalent here. Hyposensitization was limited to Bermuda and Johnson grasses with excellent results in 1949, 1950, and 1951.

Mold Allergy.—We have seen no patients from other sections of the country in whom either history or findings incriminate molds as the only discoverable or clinically significant allergens. The multiple sensitivities they possess make it very difficult to evaluate the benefit this climate offers them. Furthermore, the data from atmospheric mold studies in the Miami area are inadequate for drawing definite conclusions as to the incidence and seasonal factors of mold allergy.[7] As a result it becomes necessary, unfortunately, even with our local patients, to resort to "treatment of a positive skin test."

It is interesting to note that Alternaria, apparently the most important mold in the north, is infrequently found on our plates. The incidence of positive skin tests however, even in local patients, is higher for Alternaria than any of the other molds, probably because so many of our patients were previously sensitized in the north. The molds most frequently found on our plates are Mucor, Monilia, and Rhizopus, but Penicillium, Aspergillus, Helminthosporium, and Hormodendron are found more seasonally and are of greater significance. Gliocladium and Syncephalastrum are found frequently and seasonally on our plates but their clinical significance is unknown at this time. Our mold counts by the plate method are highest during the winter season from November to May.

There were also no cases of isolated mold sensitivity in this series of one hundred and fifty cases, yet about forty per cent of them gave positive reactions to one or more molds thought to be of clinical significance.

The prevailing ocean breeze in this area must undoubtedly be of help to these patients, but less so than with pollen cases since mold contamination readily occurs within our homes. None of the many methods for controlling moisture, and therefore mold growth, in closed spaces, have proved completely satisfactory.

SPECIFIC WEATHER ALLERGY

In the Miami area when a sharp drop in temperature (15-20 degrees below the mean average) is predicted, an allergist, with equal accuracy, may predict an "epidemic" of allergic rhinitis and bronchial asthma.[5] It is a common observation that respiratory infections as well as allergic respiratory disease, are prevalent during cold waves in Miami. This observation, plus the adequate warning system operated by the Miami Weather Bureau, has given us the oppor-

tunity to prescribe terramycin or sulfadiazine prophylactically when such a cold wave is anticipated. This has been attempted even in the absence of signs of infection. It is my impression that some patients have avoided attacks of asthma with this treatment and no apparent harm has resulted.

It is, of course, well known that many patients attribute their symptoms to weather changes while ignoring specific allergens which may operate at the same time. In these patients control of the allergic factor often minimizes the effect of changes in the weather. There remain, however, patients in whom the most careful studies and complete patient cooperation fail to reveal specific sensitivity (intrinsic asthma?). In these patients the history repeatedly indicates that attacks occur with a sudden fall (occasionally a rise) in barometric pressure, high humidity, a sudden drop in temperature, strong winds, rainfall usually when associated with a fall in temperature, and certain other elements of weather. It is interesting that many patients give a history of greater vulnerability to weather changes in an area of low altitude near the ocean and less in a geographic state of opposite characteristics. There is also an interesting corollary with those patients revealing sensitvity to specific allergens in that it is common for these "weather cases" to report much benefit for the first year or two in Miami before changes in the weather again induce symptoms. It is almost the rule for new residents to think of Miami as having continuous summer but in a year or so they recognize definite seasonal variations.

There are two distinct seasons in Miami running from May to November and from November to May with April, May, October and November being transitional months. The winter season from November to May is characterized by having a 10 per cent mean increase in wind velocity with proportionately greater indicence from the north and northwest. It is therefore the cool season with a mean temperature of 70.3 degrees as opposed to the average of 80.0 degrees in the summer. The mean humidity is lower, the barometric pressure usually higher, and the dew point is at a low level. The summer season from May to November has, in a general way, opposite characteristics.[12] Much more study is needed, and is in progress, concerning the specific changes in weather and their relationship to the allergic state. The relation of humidity to certain dermatological conditions in the Miami area has recently been described by Sams.[11]

In this group of one hundred and fifty cases fully 70 per cent of them were affected in some degree by weather changes in their original homes as well as in Miami, but only thirteen presented this factor as the only discoverable etiology in the production of their symptoms. Twelve were affected during the winter season and one during the summer. Four of the winter cases received little or no benefit from symptomatic treatment and it was arranged for them to go to Arizona. All four patients were completely relieved and one has made his permanent home there. However, it was recently learned that one of these patients had a recurrence during her second year of residence in Tucson. In these four patients it was reasoned that, since allergens did not play a recognizable part, a change from a low damp seacoast area to one of opposite characteristics would be of value. It has been observed, on occasion, that the reverse is also true.

ENVIRONMENTAL ALLERGY

Fifty-nine of the one hundred fifty patients were found to be sensitive to household or environmental allergens acting as a primary cause of their symptomatology. It was not logical to expect, nor did it occur, that moving to Miami would result in allergic control or a clinical cure.

In some patients temporary improvement occurred and was most likely explained by the general characteristics of this area. This is a relatively new community utilizing modern construction with good ventilation a primary object. Furnishings by modern standards avoid the heavy concentration of household inhalants. Drapes, for example, are usually of light washable materials and never hung over the windows where they can be exposed to constant wind currents. Overstuffed furniture is avoided with much use of bamboo, plastics and washable woods. Flooring is usually concrete, marble, terrazzo, or tile, with few rooms requiring wall-to-wall carpeting. The result, therefore, is a lower concentration of household inhalants which, though difficult, can be accomplished anywhere. The lack of industrial dusts in this area and the usual psychological advantages of a change in environment must also play a part. It is important to note that in most cases these advantages served to give the patient a false sense of security, since improvement lasted a short time (rarely more than two or three years) before they again developed symptoms from old or newly acquired sensitivities.

Closer analysis of the fifty-nine environmental cases permits further subdivision; seventeen of them had been successfully treated at home, thirty-five had been unsuccessfully treated, and seven had inadequate treatment.

The experiences of the seventeen successfully treated patients seem of great importance. Four of them continued treatment for one year after establishing residence. At the end of that time they discontinued treatment but practiced strict avoidance of known allergens and have remained well. Four others continued maintenance treatment and also continued to be well. It is the author's impression that treatment for one year in a new climate represents proper and cautious management but that prolonged maintenance of a successful hyposensitization program is preferable. The remaining nine patients of this group felt so well on arrival that treatment in all respects was discontinued. All of them suffered recurrences within a range of four months to three years. An example of interest follows:

Case No. 1003 (S. S.) A seventeen-year-old boy presented a history of bronchial asthma with onset after a respiratory infection in New York at the age of four years. He was found sensitive to pollens, animal danders, house dust, chocolate, and chicken. Results from treatment were very good but in the hope of gaining more permanent benefit he visited Arizona in 1946. He continued treatment with maintained improvement and it was suggested that he remain there at school. He, however, preferred to come to Miami and throughout 1947 and 1948, while living in the dormitory, he continued to be well without maintenance therapy. At the end of the school year in 1948 he moved to a Beach hotel and immediately developed severe and persistent asthma. Complete relief was obtained by an environmental change although the specific exciting agent was not found.

The thirty-five unsuccessfully treated patients and the seven who had received inadequate care presented frustrating problems. Of the total number of 42 patients, 22 failed to have consistant relief and eventually all of them were subjected to further studies but remained intractable. Fifteen of the unsuccessfully treated patients and five of the inadequately treated patients were considerably helped by the isolation of specific causative factors previously unrecognized.

Nonspecific irritability of the bronchial tree eventually superimposed on prolonged and uncontrolled specific sensitivity often obscures the diagnosis in these environmental allergies. This observation plus the fallacy of attributing improvement in environmental allergy to climatotherapy is well illustrated in the following case.

Case No. 93 (L. S.) A fifty-nine-year-old woman had initial symptoms of respiratory allergy in Chicago at the age of thirty-four years. This attack was apparently due to an environmental allergen neither searched for nor recognized but her symptoms disappeared when she moved to another part of the same city. She was then well for five years, the last two being spent in Newark, N. J. At thirty-nine years of age she moved to East Texas where she lived on a farm for one year and suffered continuous asthma. She moved to Dallas, Texas where she was completely well for twelve years until she moved to another house in the same city. It became necessary for her to move again so she returned to Chicago where, for the first time, seasonal ragweed symptoms appeared. For some reason she was tested only for the pollens and received ragweed hyposensitization with poor results so she moved to Miami Beach. Her symptoms continued and a complete survey was performed revealing sensitivity to ragweed, Alternaria, Fusarium, pyrethrum, cat and dog dander. Under specific treatment she did well from 1946 to 1949. At this time for unexplained reasons but associated with changes in the weather, exposure to fresh paint, and other nonspecific irritants she had a recurrence of severe asthma and returned to Chicago.

FOOD ALLERGY

Patients with specific food sensitivity do no better in the Miami area when ingestion of the allergen is permitted. Only four patients in this group of one hundred-fifty cases revealed positive skin reactions to foods, with clinical correlation, as the only discoverable cause of their symptoms. However, twenty-two patients were found to have food allergy in addition to other important sensitivities. The ingestion of an allergenic food was often unrecognized, sometimes a result of negligence, and rarely unsuspected by the patient.

The beneficial affect of dry inland environment and particularly high altitude on food sensitivities has been reported.[13] In this area of opposite characteristics the reverse situation of increased clinical sensitivity to foods was not observed.

INTRINSIC AND INFECTIOUS ALLERGY

Patients with allergic rhinitis and bronchial asthma generally classified as the "intrinsic" or "infectious" type usually do better in the Miami area. This is principally due to the fact that bacterial infections of the respiratory tract are somewhat less frequent and definitely less virulent than those of the north. This observation is of importance in all types of respiratory allergy. Avoiding prolonged cold weather and inclement changes of weather is also beneficial, as is the psychotherapeutic effects of environmental change. The so-called virus in-

fections, however, are prevalent and on the increase here as in other sections of the country. It is important to note, that when the eleven patients of this type in this series of one and fifty patients did acquire respiratory infections in this area, the same symptomatology occurred as at home. Since these patients came under my care it is obvious that their improvement was only quantitative in type.

PREDISPOSING FACTORS

An allergic individual with specific sensitivities that are recognized and adequately treated may not have a satisfactory response until previously unrecognized predisposing and contributory factors are diagnosed and treated.[5] A change in climate can be of no value to this type of patient. The complicating diseases in this series were hypothyroidism, hyperthyroidism, hyperinsulinism, pulmonary tuberculosis, diabetes mellitus, and hookworm infestation. Nine of the one hundred fifty patients reviewed illustrated this principle as shown in the following case:

Case No. 655 (E. F.) A thirty-seven-year-old man reported onset of eczema and asthma in Toronto, Canada at the age of eleven years. Histamine injections, elimination of lamb from the diet, and avoidance of cat hair gave a fairly good response. In 1940 for business reasons, the family moved to Miami and the patient was well for about a year before noting the return of mild and infrequent asthma in the early mornings. In 1945 he acquired a dog and soon suffered severe asthma. An allergic survey at this time revealed marked positive reactions to house dust, feathers, cat and dog hair. Dust hyposensitization and environmental control had no value. An additional history was then obtained that the patient had hookworm disease in Brazil in 1943 with supposedly good results from treatment. It was also learned that at the time of this infestation his asthma was very severe. Hookworm ova were found in the stool and eliminated by a course of tetrachlorethylene, followed promptly by disappearence of his asthma. He has remained free of asthma since 1946 although two additional courses of anthelmintics were necessary. No hyposensitization has been given but the patient strictly avoids animal danders and follows the usual dust precautions.

COMPLICATIONS OF ASTHMA

Complications associated with prolonged bronchial asthma of any type (usually infectious) such as emphysema, bronchostenosis, bronchiectasis, cor pulmonale, and sinusitis, which represent irreversible pathological changes, show little if any improvement in the Miami area. However, the four patients in this series received some benefit for the same reasons considered under the heading above of "Intrinsic and Infectious Allergy." The suffering of these patients may be less in frequency and duration but under adverse conditions their symptomatology will occur as at home.

OTHER ALLERGIC SYNDROMES

In comparison with the respiratory forms of allergy previously discussed, it is even more difficult to evaluate the influence of climatotherapy in the sixteen patients in this series with eczema, chronic urticaria, migraine, migraine equivalents and histaminic cephalgia because there are many other prominent factors besides allergy involved, particularly from the psychosomatic point of view. In most patient with allergic disease, the relief from nervous tension, chronic nervous exhaustion, parental influence and control, conflicts with other members

of the family group, separation from home, school or business responsibilities account for much temporary improvement. It is logical that this improvement is enhanced when there is also a change in climate as well as environment.

There were, however, only eight patients in the entire series in whom the psychic factor was considered the primary problem. Such a diagnosis must be made with great caution and one must not fail to consider the recent survey demonstrating control of behavior problems in children by eliminating allergic intoxication.[14] This psychsomatic factor in allergic disease, incidently, poses another great responsibility for the physician as exemplified by the following case, even when climatotherapy is effective.

Case No. 811 (L. S.) An eight-year-old girl presented lesions of atopic eczema with the usual distribution. In Kansas City, Missouri, during infancy, she developed eczema due to foods, rapidly controlled by avoidance therapy. At three years of age she had a return of the eczema with allergic rhinitis thought to be due to dust sensitivity. At four asthma first appeared with a respiratory infection. All her allergic manifestations became progressively worse and two years later the family was advised to move to Miami. She did well until shortly before coming under my observation. Careful allergic management was of no value but it was soon learned that their move to Miami caused many changes in the family group. The father, previously a successful businessman, was repeatedly unsuccessful in re-establishing himself here. The patient became a model and worked unusually hard so that her sleep and rest were inadequate, but her income was most necessary. Emotional tension and unhappiness in the entire family were obvious and marked. Under these circumstances successful treatment was neither anticipated nor obtained.

Certain other observations from the point of view of climatotherapy warrant consideration in a study of eczema, urticaria and the migraine group. It is a fairly common observation that hot and humid weather with a falling barometer results in increased attacks and attacks of greater severity in the migraine group. We therefore see more of these cases in the summer months. It is apparent in eczema, as in the group of respiratory allergy, that a sudden fall in temperature is associated with an exacerbation of the disease. The exacerbation is usually directly proportional to the degree of fall in temperature. Eczema, and to a lesser extent urticaria, is often benefited by a mild erythema from direct sun exposure. Yet there is a point of tolerance after which these patients are made worse and there are some patients who are improved when sun exposures are avoided. Proper control of sun exposures in addition to local, allergic, nervous, and systemic treatment makes climatotherapy successful in these conditions. To the consideration of sunlight, which is an important factor in climatotherapy in the Miami area, must be added the problem of photosensitivity as shown in the following case:

Case No. 1133 (S. H.) a twenty-one-year-old woman, presented the complaints of itching, swelling, and eczematous lesions of the lower face most marked on the lips. It was suspected in New York that this was a lipstick sensitivity but patch tests were negative. When she avoided the use of lipstick, except occasionally at night, she was well. While attending the University of Miami an obvious social problem develcped and her symptoms returned. A 3 per cent Bromo Acid patch test on the skin in the collar area was negative but became definitely positive when repeated with exposure to sunlight. A nonpermanent lipstick made by the Texas Pharmacal Company was a complete solution to this problem of eczema and photosensitivity.

TABLE I. SUMMARY OF 150 CASES STUDIED

ETIOLOGICAL GROUP	PRIMARY AND/OR SIGNIFICANT FACTORS	NUMBER OF SENSITIVITIES	IMPROVEMENT FOLLOWING RESIDENCE IN MIAMI			NUMBER OF CASES TREATED	IMPROVEMENT FROM ADDITIONAL TREATMENT			CASES DISCONTINUING TREATMENT IN LESS THAN SIX MONTHS
			PROLONGED	TEMPORARY	NONE		PROLONGED	PARTIAL	NONE	
Airborne inhalants	Ragweed	20	16	4	0	4	2	1	0	1
	Trees	7	0	6	1	7	5	1	0	1
	Grasses	9	0	7	2	9	7	1	1	0
	Molds	58	15	15	28	43	22	7	6	8
Weather	All types	13	3	9	1	13	3	3	4	3
Environmental	Household inhalants	59	8	32	19	59	21	12	18	8
Ingestion	Foods and drugs	22	0	0	22	22	15	4	2	1
Intrinsic	Unknown	11	0	9	2	11	0	2	5	4
Predisposing and contributory factors	See sections	9	0	0	9	9	8	1	0	0
Complications	See section	21	0	4	17	4	0	4	0	0
Psychosomatic	Multiple	8	0	2	6	8	1	2	3	2
	Totals	237	42 (17.7%)	88 (37.1%)	107 (45.2%)	189	84 (44.4%)	38 (20.1%)	39 (20.6%)	28 (14.9%)

DISCUSSION

It is obvious that none of the one hundred fifty patients studied for this paper obtained allergic control with complete and prolonged relief of symptomatology solely by becoming semi-permanent or permanent residents of the Miami area. These patients were accepted for this study because the onset of their allergic disease occurred previously in other sections of the country. The fact that they were seen in private practice here clearly shows their need for additional treatment. All these patients either continued their symptoms in some degree or developed recurrences in from four months to five years with the most common latent period being two years.

There undoubtedly is a group of patients of undetermined number, suspected by the author to be small, who obtained complete and prolonged relief by residence in this area. It is equally obvious that such patients would not be seen in a local allergy practice and therefore the importance and size of such a group must be judged from records of allergists outside this area.

For the purpose of determining the value of climatotherapy in the Miami area it is best to consider the primary or significant sensitivities rather than the actual number of patients. It is agreed by all allergists that mixed causes are the rule in most allergic syndromes. This was adequately demonstrated in the summary of these one hundred fifty patients (Table I) by the fact that two hundred thirty-seven factors were isolated as etiological agents. Many more etiological agents were found but were not considered either primary or significant.

Grading patient improvement, as a result of residence in Miami, into divisions of "Prolonged," "Temporary," and "None," presented a difficult problem since there was so much overlapping. For example a patient may come to Miami and have complete relief for a short time, then have a return of symptoms but still be better than at home, and finally revert to the same severity of the disease he previously suffered. Every attempt was made therefore, to classify these patients by combined subjective and objective evidence. It will be noted that forty-two or 17.7 per cent of the two hundred thirty-seven sensitivities received prolonged benefit by residence in Miami but thirty-one or 13.0 per cent of these were in the ragweed or mold groups. (Table I.) This would indicate that for this group of one hundred fifty cases the benefit from climatotherapy was, at best, purely quantitative.

The number of sensitivities treated depended upon the clinical indications and the willingness of the patient to cooperate. The results by tabulation are self-explanatory. The number of patients discontinuing treatment in less than six months are tabulated in the last column but many more of those receiving additional treatment with partial control or no benefit discontinued such treatment within a year. All other tabulated cases were under observation for at least two years.

SUMMARY AND CONCLUSIONS

This paper presents a study of the effect of climatotherapy upon one hundred fifty known allergic individuals who came to the Miami area for an ex-

tended period of time. From the data presented 17.7 per cent obtained prolonged relief as explained in the discussion, 37.1 per cent had temporary benefit, and 45.2 per cent noted no improvement. The various etiological factors were discussed with particular reference to this area. Specific treatment was given as indicated and the results tabulated.

It appears that the value of climatotherapy is acclaimed during the early transition period by the small percentage of patients who receive benefit. Observation over a longer period of time indicates that treatment based on climatotherapy without individualization is doomed to fail. In this series of cases all of them suffered relapses within four months to five years with the most common latent period being two years.

The patient who improves with hospitalization, environmental change, dietary restrictions, and other forms of specific treatment does not need climatotherapy and must not seek it as a sole method of treatment. Black certainly summarized the question of climatotherapy a few years ago by saying, "Unless one knows from what he is running away his move is a definite gamble; if he does know he should be able to take care of it at home."[15]

Climatotherapy in the Miami area should be considered the indicated method of treatment under the following conditions: (1) When careful and complete studies have failed to relieve the patient. The financial status of the patient should be adequate to make this change. He must be made aware of the possibility of failure and the need of at least one year as a trial period before conclusions are drawn. (2) When the patient is benefited mostly or entirely by atmospheric conditions created by modern methods of humidity and temperature control to simulate Miami. It becomes apparent that allergists need the cooperation of meteorologists and the information they can provide. In this phase of allergy the meteorologist becomes as indispensible as the botanist in pollen allergy. Uniform techniques for studying the effects of "weather" on allergic patients need to be devised.

Climatotherapy in the Miami area should be considered an adjunct method of treatment under the following conditions: (1) Seasonal pollen and mold allergy not controlled by adequate specific therapy. (2) To break a persistant state of allergy so that proper procedures for diagnosis and/or treatment can be instituted. (3) As an adjunct to treatment. For example, after a Caldwell-Luc operation is performed for sinusitis in infective asthma and it is imperative to avoid further infection to obtain good healing before attempting allergic studies and treatment. (4) To obtain a quantitative reduction of bacterial infection of the respiratory tract. Some patients are markedly improved but it must be noted that so-called virus infections are also prevalent here. (5) To minimize the effects of prolonged cold weather. (6) Where sun exposure will be of benefit. (7) Pyschotherapeutic reasons. The patient in allergic balance should continue specific therapy and all precautions as at home.

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POLLEN COUNTS: VARIABILITY AND PERCENTAGE ERROR IN A GIVEN LOCATION UNDER STANDARD CONDITIONS

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THE variability of pollen counts obtained from stations within the same general locality was noted during pollen surveys that were carried out as part of a ragweed pollen exterminating program in the Philadelphia area during the years 1947-1950 inclusive. Deviations of this type have been attributed to such diverse factors as direction and velocity of winds, proximity to sources of ragweed pollen or large bodies of water, local precipitation of moisture, etc. Some of our stations,[1] however, were within a short distance of one another (½ to 1 mile) and should have precluded or reduced to a minimum the factors responsible for the variations in atmospheric pollen concentration. Furthermore, the shelters were all exposed under the standard conditions set forth by the Committee on Aeroallergens of the Research Council of the American Academy of Allergy.[2] Despite these precautions, the counts from nearby stations showed a higher degree of variability than warranted by the circumstances. This observation raised the question of the constancy and accuracy of pollen counts at a given location under standard conditions. How accurate were pollen counts? What factors contributed toward their fluctuation? The following experiment was set up to answer some of these questions.

PROCEDURE

Three standard pollen shelters were mounted adjacent to one another on a wooden platform and placed at an unobstructed site atop the roof of Mt. Sinai Hospital in Philadelphia. The slide area in each shelter was placed in a different direction to determine the effect of wind direction on precipitation of pollen; thus, the slide in the first shelter lay in an east-west direction; that in the second shelter, in a north-south direction, while in the third shelter it faced a northwest-southeast direction. The shelters themselves were in a straight line, about two feet apart. The roof was flat and entirely unobstructed to rule out the possibility of wind currents which might be set up by high walls, balconies or other nearby wind-reflecting surfaces. Since part of the variability could be explained by uneven distribution of pollen on the slide, it seemed advisable to determine the degree of correlation between corresponding areas on the same and different slides. Each slide, therefore, had three 3.6 square centimeter areas etched onto the glass. The center areas were 1.9 cm. square while the end areas measured 2.5 by 1.44 cm. A diagram of the slide areas and directions in which they faced is illustrated in Fig. 1. The slides were coated with a thin film of petroleum jelly and were exposed daily for a 24-hour period during each of the 47 pollinating days of the 1949 ragweed season. The marked areas were examined with-

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out staining and the number of ragweed pollen granules in each area were counted. All the counting was done by one individual (J. S.). For each day, therefore, there were three counts on each of three slides, or a total of nine counts. At the conclusion of the season the material was subjected to statistical analysis.

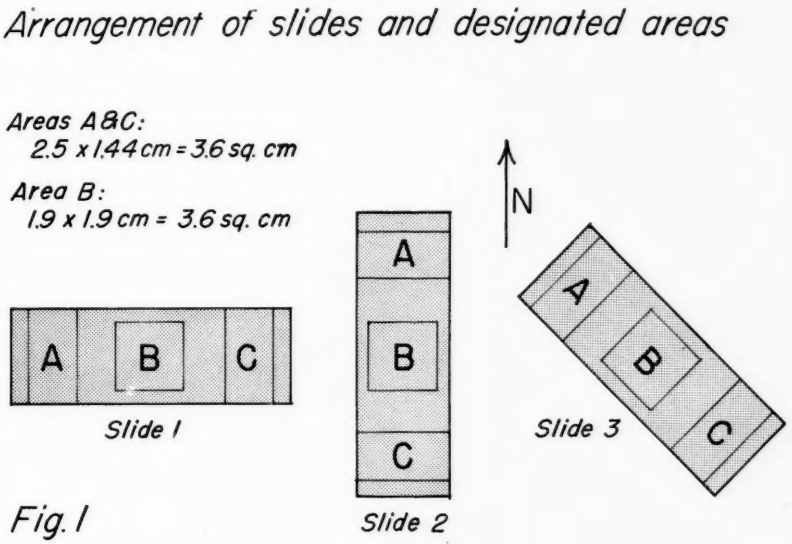

Fig. 1

RESULTS

The constancy of pollen counts on different areas of the same slide was determined by plotting in a graphic form the daily counts from each area of the slide. Inspection of the graph (Fig. 2) shows almost identical daily counts and the plotted curves of each area almost overlaying one another. Thus, there is a high degree of correlation between the counts obtained from different areas of the same slide. The graph itself is rather typical of the pollen curves obtained in the Philadelphia area. There were several days between August 27 and September 4th on which the counts varied more than usual. These were days when the pollen counts were relatively high and it is possible that the presence of large clumps of pollen could account for this discrepancy and for the deviations in the graph.

The next procedure was to determine the degree of correlation between counts on adjacent slides. This was accomplished by first obtaining an average daily count for each slide and then plotting them in graphic form. The results are illustrated in Fig. 3. As in the first study the degree of correlation is marked, with minor variations on the same days as in the first study.

The total counts for the season for each area were determined by adding the daily counts. These figures are shown in Fig. 4. The total season counts are extremely close, ranging from 3710 to 4158 for the 47 days, with an average of 3884 for all nine areas. Also shown in this table is the average count for each area of three slides, for all days of the period. These were obtained by

dividing the total counts by the number of days (47) and varied from 77 to 91, with a mean of 83. The mean deviation was 81 and the standard deviation, as figured by the root mean square formula was 100. The probable error was 9.8 or a mean of 83 ± 9.8. It may be concluded from the above charts and figures that a high degree of correlation exists among the three slides and the individual areas on these slides.

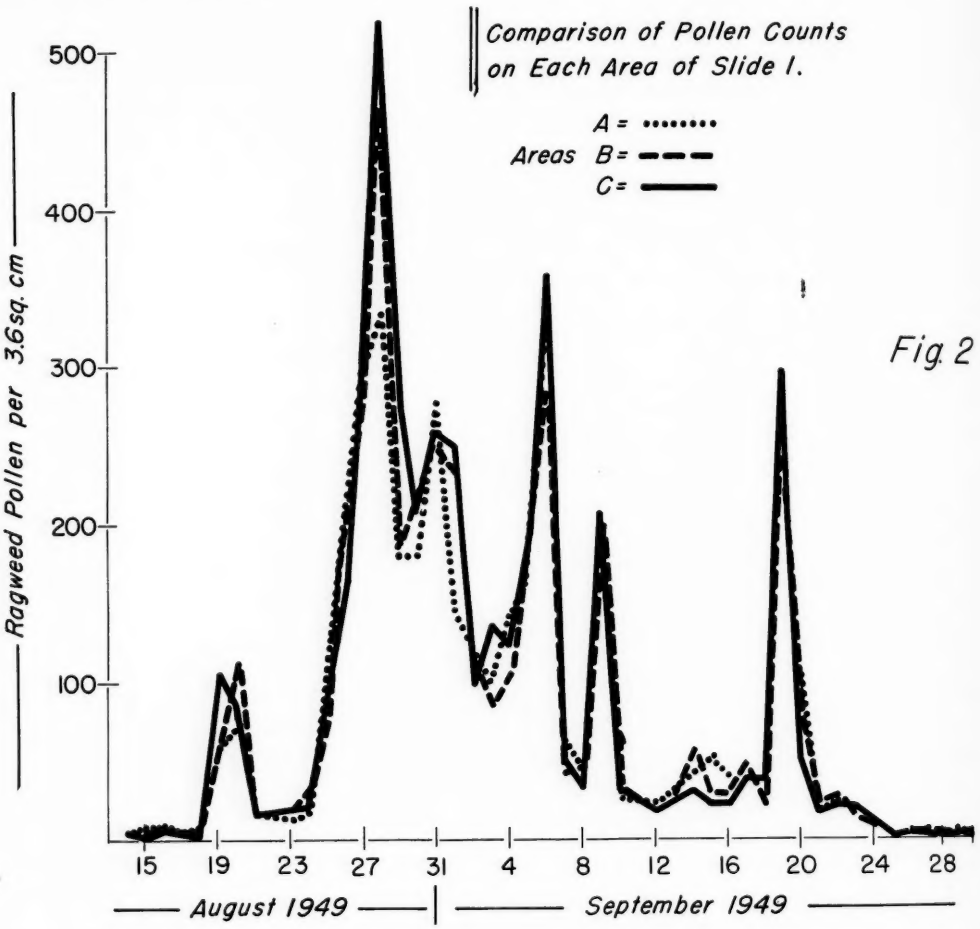

Fig. 2

DISCUSSION

It is evident from these studies that pollen is evenly precipitated and distributed on slides which are exposed under the standard conditions recommended by American Academy of Allergy. One could, therefore, count any area of a given slide and be certain that the count is characteristic of the entire slide when the probable error is taken into consideration. Furthermore, there was a high degree of uniformity between counts on adjacent slides, showing that counts obtained at a given point were accurate estimates of the pollen concentration at that location. It must be pointed out that the location of the

shelter and its proximity to wind reflecting surfaces is of the utmost importance. This same experiment was conducted in 1948 but the shelters were situated within 10 feet of a balcony where wind currents and reflection occurred. The counts within one shelter were fairly uniform but varied considerably from those obtained in adjacent shelters. Such lack of correlation spoke either for the lack of standard conditions or for an unreliable method of atmospheric pollen counting. After discussing our bizarre results with several members of the pollen committee it was decided to withhold publication of our results until the exact cause of the discrepancies was found. The uniformity of the results with a new and unobstructed location attests to the need for adherence to the standard prescribed conditions. Furthermore, it corroborates the accuracy of this method of atmospheric pollen sampling.

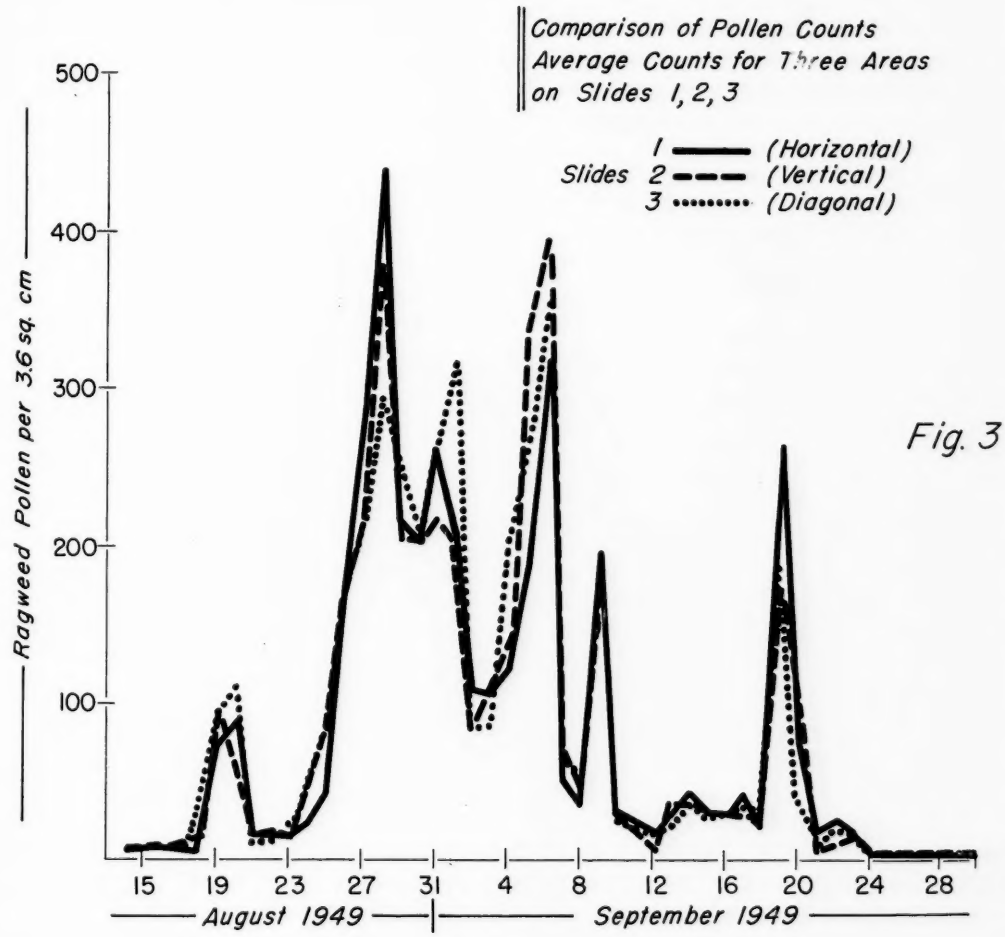

Fig. 3

During the period in which the 1949 experiment was conducted wind velocity and direction was variable. However, despite the inconstant meteorological conditions, the distribution of pollen on the slides was uniform. There

was no excess on the edges of the slide, in the direction from which the wind originated, nor did there seem to be any variability on the slide areas when the wind velocity was greatest.

STATISTICAL ANALYSIS OF POLLEN COUNTS

	TOTAL COUNT FOR ALL DAYS OF PERIOD (47 DAYS)	AVERAGE COUNT FOR ALL DAYS OF PERIOD (TOTAL ÷ 47)
SLIDE 1 AVERAGE	3913	85
Area A	3710	81
Area B	3856	84
Area C	4158	90
SLIDE 2 AVERAGE	3803	81
Area A	3636	77
Area B	3898	83
Area C	3884	83
SLIDE 3 AVERAGE	3922	83
Area A	3874	82
Area B	3962	84
Area C	3924	83
ALL SLIDES AVERAGE	3884	83

Mean = 83.
Mean deviation = 81.
Standard deviation = 100.
Probable error = 9.8.

Fig. 4.

SUMMARY

A study was made of the deviation of pollen counts on different areas of the same slide and on other adjacent slides. When subjected to statistical analysis* a high degree of correlation was found between any and every one of these areas, regardless of the direction in which the slide was placed or the slide area which was counted.

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*Statistical analysis was done by Frank J. Fete, A.B., M.A.

COMPARATIVE SKIN TESTING IN THE ANTECUBITAL AND POPLITEAL SPACES

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IT IS well recognized that the antecubital and popliteal spaces are favorite sites for atopic dermatitis, but a search of the literature has not revealed any adequate explanation for this finding. In 1920, Schloss[1] using the scratch test on the forearm found that the nearer the test to the elbow fold, the larger the reaction obtained. Larsen, Paddock, and Alexander[2] in 1932 first reported testing in the antecubital area. They found that in 14 ragweed sensitive patients, tests done in the elbow fold were never smaller and were usually larger than tests introduced 10 cm. farther down on the forearm. Tests with histamine are not reported. Because of this paucity of information, it seemed worthwhile to explore further the responsiveness of the crease areas using both specific and nonspecific urticariogenic excitants.

TECHNIQUE

Because of the unusual character of the skin in the crease areas, considerable preliminary testing was done before it was possible to develop a reliable testing technique. Injection of the testing solutions as close as possible to the surface of loose wrinkled skin was found to be the most important factor in the performance of this technique.

Over 150 subjects ranging in age from 12 to 70 years were studied. An approximately equal number of males and females were used. Most of the atopic patients were receiving treatment for hay fever. They had been carefully selected to eliminate subjects with skin disturbances. All testing was done in sites well away from treatment areas. The nonatopic patients were individuals who were being used as recipients for passive transfer studies and had been thoroughly screened to rule out allergy.

Histamine base in the dilution of 1-10,000 was the nonspecific excitant used to produce whealing. The atopens employed in the sensitive subjects were nonirritating and were used in a strength which would produce specific positive reactions of slight to moderate size (.7 to .8 cm. in diameter) since Bowman[3] has shown that reactions of this size are the most desirable for comparative testing. Tests in the crease areas were always done approximately 1 cm. above or below the crease of the antecubital or popliteal space while the comparative test on the arm or leg was made from 15 cm. to 20 cm. above or below the crease area. Both the medial and lateral sides of the extremities were studied, but with due regard to Bowman's observation[3] that the medial surface was more active than the lateral. Thus tests in the medial or lateral parts of the crease area were compared to tests in corresponding positions on the arm or leg.

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Since the skin of the upper arm is most commonly employed for routine intracutaneous testing, the major portion of the investigation was devoted to a comparison of tests in this region and in the antecubital area.

RESULTS

The results obtained in comparative testing of the antecubital area and the arm with histamine and allergens are listed in Table I.

TABLE I

SUBJECT	EXCITANT	TOTAL NO. OF COMPARATIVE TESTS	NO. OF CASES SHOWING LARGER REACTIONS IN CREASE AREA	NO. OF CASES SHOWING LARGER REACTIONS ON ARM	NO. OF CASES SHOWING EQUAL REACTIONS AT BOTH AREAS
Atopics	Histamine 1:10,000	63	48 (76 per cent)	8 (13 per cent)	7 (11 per cent)
Nonatopics	Histamine 1:10,000	35	23 (66 per cent)	6 (17 per cent)	6 (17 per cent)
Atopics	Atopens	40	33 (83 per cent)	3 (7 per cent)	4 (10 per cent)

A similar tendency toward greater reactivity in the crease area was observed on comparative testing of the forearm and the antecubital area.

The same results were also obtained with histamine and atopens in comparative tests involving the popliteal area, as listed in Table II.

TABLE II

	IN PATIENTS TESTED WITH HISTAMINE		IN PATIENTS TESTED WITH ALLERGENS
	ATOPICS	NON-ATOPICS	ATOPICS
Number of cases showing larger reactions in crease area	10	4	11
Number of cases showing larger reactions above crease area	1	1	0
Number of cases showing larger reactions below crease area	0	0	2
Number of cases showing equal reactions at both areas	2	0	1

DISCUSSION

Fewer comparisons were made on the crease area of the leg than on the arm since the results were decisive both with specific and nonspecific excitants. In comparative tests done simultaneously on the upper and lower extremities of the same individuals, the wheals in the antecubital and popliteal spaces gave practically the same measurements. Atopic individuals tended to show increased whealing in the crease area both to histamine and allergens. Thus a patient who was tested simultaneously with a pollen extract in one arm and with histamine in the other usually displayed crease hyper-reactivity in each arm.

One patient, who was born with a paralyzed arm that had never been bent, showed increased reactivity in the crease area of the paralyzed as well as of the normal arm.

The author was able to confirm the findings of Bowman[3] who showed that responsiveness to histamine increased as tests were introduced progressively down the arm, whereas responsiveness to atopens diminished under the same circumstances. The crease area, however, was not included in these comparisons.

The factors responsible for the increased reactivity of the crease areas of the extremities are not well understood. Little is known about differences in the physiological or anatomical make-up of these sites which could influence capillary permeability.

Tuft, Tuft, and Heck[4] have recently demonstrated increased reactivity of the sweat glands in the areas developing atopic dermatitis. They showed that intramuscular Benadryl could block this response and that after the dermatitis was far advanced, exposure to offending allergens could no longer produce sweating in these sites. In studying the PH of the skin or the secretion of the skin, Blank[5] found that the antecubital fossa consistently had the most acid PH of any skin area of the body. Bernstein, Herrmann[6] and others, who have studied the PH of diseased skin, have found that in certain disorders such as eczema, the PH in the affected area tends to be more alkaline. These findings may have some bearing on the localization of atopic dermatitis but their mode of action is not clear.

Hyper-reactivity in the creases following both specific and nonspecific excitation has been demonstrated. An adequate explanation for this observation, however, has not yet been found.

SUMMARY

1. In both atopic and nonatopic individuals, skin tests with histamine produced larger reactions in the antecubital fossa than on the arm or forearm. A similar but even greater difference was observed in atopic subjects when tested in this manner with atopens to which they were sensitive.

2. Skin tests with histamine performed in the popliteal space in both atopic and nonatopic individuals showed a pronounced increase in reactivity as compared to sites either above or below this space. The differences were even more pronounced when comparative skin tests were made with atopens.

The author is indebted to Mr. Joe Lowe of New York City for financial assistance which helped to make this research possible.

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PURPURA SIMPLEX DUE TO ANTIHISTAMINIC DRUGS

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THE ever-increasing use of the antihistaminic drugs has resulted in a constantly growing list of recorded side effects. From time to time excellent reviews on the status of antihistamine therapy have been published by Loveless,[1] Feinberg,[2] and others. Earlier papers stressed the side effects referrable to the central nervous system and the gastrointestinal tract, most of which were comparatively mild in character. With the constant increase in the use of these drugs, however, there began to be reported a variety of side effects of a more serious nature. It is not my purpose here to enumerate these toxic effects. A very comprehensive review of the subject was compiled recently by Wyngaarden and Seevers.[3] Included in their article are cases of convulsions, toxic psychoses, hemolytic anemias, agranulocytosis, and a review of eleven fatalities.

I have had under observation for some time now, a case of purpura simplex caused by ingestion of antihistaminic drugs. Although this case in no way presents the severe picture of the blood dyscrasias previously reported, I thought it would be of interest to record it as an example of one more reaction to antihistamine therapy.

CASE REPORT.—V. S., a 44-year-old white woman, was referred for the treatment of asthma in February, 1947. She gave a history of ragweed hay fever and asthma of 9 years duration, for which she had never had specific treatment. Asthma would also occur during the winter with or following upper respiratory infections. The present attack began with a "cold" some 2 months previously and had been alternately mild and severe since that time. She had taken no medication except Pyribenzamine, one 50 mg. tablet thrice daily for 3 days at the onset of the cold, but had stopped the tablets because of the appearance of small black and blue spots on her legs. She stated that this had also occurred in September when she had taken 3 tablets daily for 3 days for relief of hay fever. After stopping the tablets, the spots disappeared in 10 days after regressing through brown, green and yellow stages.

Physical examination revealed a pale nasal mucosa, and many sonorous sounds throughout both lung fields. There were 10 to 12 small purpuric areas 2 to 5 mm. in diameter on the anterior tibial surfaces of both legs. Urinalysis was normal. Kahn test was negative. The blood count presented these normal findings: hemoglobin, 13 Gm. per cent, red blood cells, 4,500,000, white blood cells, 7200; a differential count of polymorphonuclears, 70 per cent, lymphocytes, 27 per cent, and eosinophiles, 3 per cent. A platelet count showed 400,000 per c. mm., bleeding time was 2 minutes, coagulation time was 6 minutes. The tourniquet test was negative.

Intradermal tests showed marked reactions to house dust and feathers, and a moderate reaction to ragweed pollen extract. Elimination of feathers, maintenance of a dust-free bedroom and one Tedral tablet morning and night

brought quick relief. Within a week, medication was not required, and in 10 days the purpuric spots had progressed through their various stages and had disappeared.

Hyposensitization with ragweed and house dust extracts, and bacterial vaccine was begun and upon reaching maximum dosage was continued on a perennial basis. She remained under treatment until April, 1950, during which time she was entirely free of both hay fever and asthma. At this time, having been well for 3 years, the patient decided to stop treatment. She continued to be well until early September, when hay fever symptoms developed. She was induced to try Pyribenzamine again, this time taking ½ tablet (25 mg.) after meals and at bed time. Similar purpuric spots developed after taking the tablets for 3 days and cleared up in 10 days after discontinuing medication. Hematologic findings during ingestion of tripelennamine were entirely normal. Inasmuch as she was still having nasal symptoms, she was given Benadryl, one 50 mg. capsule thrice daily. She took these for 10 days with relief of her symptoms and no appearance of purpura.

During the past winter she had several upper respiratory infections. For one of these she was given Thephorin 25 mg. four times a day without developing purpura. On another occasion she took Neohetramine 25 mg. four times a day for a few days and noticed the appearance of a number of purpuric spots on her legs.

DISCUSSION

Recently, Adams and Sacca[4] reported a case of allergic purpura that cleared up rapidly under antihistamine therapy and remained symptom-free while taking Chlor-trimeton, without eliminating foods that were shown to be causative agents in the production of purpura. The case here reported presents the opposite picture, namely, the onset of purpura from ingestion of several antihistamines. That the same agent in different patients can produce diametrically opposite effects is well known, as witness either sedation or excitability, constipation or diarrhea in different patients from the same antihistamine.

That some antihistaminic drugs will cause side effects, while others will not, in the same patient has been amply demonstrated by Sherman and Cooke[5] and by Seyler.[6] Apparently the chemical structure of the product used is the important factor in whether or not side effects will develop in the susceptible individual. This explains why Pyribenzamine and Neohetramine, which are related structurally, caused purpura in the case here described, while Benadryl and Thephorin, both of which have different chemical formulas, did not produce purpura.

While many of the more severe toxic side effects are due to overdosage or prolonged use of the antihistamines, it is nevertheless evident that the milder and less severe reactions can occur with average doses taken for but short periods.

SUMMARY

1. A case of purpura simplex from ingestion of antihistaminic drugs is presented.

2. In the same patient, some of the antihistamines may cause purpura, while others may not.

3. The dose of the drug used need not be excessive, nor need it be used for an extended period to produce this effect.

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SUBCUTANEOUS EMPHYSEMA IN BRONCHIAL ASTHMA

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TO THOSE physicians who are primarily interested in chest diseases and thoracic surgery, the presence of subcutaneous emphysema does not usually produce great alarm. Occasionally it becomes a distressing symptom and requires active therapy; but in general it is seen and accepted as a minor complication of the various thoracic procedures. Therefore, in a busy practice where frequent asthma is seen, the appearance of subcutaneous emphysema in a case of asthma did not produce any alarm. But on second thought it occurred to me that I had never seen a case of subcutaneous emphysema complicating asthma. Therefore, a brief review of the literature was made and it was found that it is indeed a rarity. In fact, up until 1945 there had been only 26 cases reported in the literature, and through March, 1951, there have been 73 cases of spontaneous subcutaneous emphysema occurring but only 28 of these were listed as complicating asthma. In view of this fact I have decided to present this case in order that it may be tabulated with future reports.

CASE REPORT

Mr. L. C. L. is a 49-year-old white, married male who is a carpenter by trade. His history revealed that he had had recurrent attacks of asthma for a period of twenty years. Each year the attacks become more frequent and more severe. The present attack began three weeks before admission to the clinic. In addition to his asthma he gave the history of perennial hayfever. His family history revealed that his father had asthma and he had a brother and sister, both of whom had asthma.

He was admitted on May 1, 1951; at that time he complained bitterly of pain under the sternum and around his neck. He felt that he was choking. In fact, it was this symptom that brought him to the clinic because it was different from those of his previous attacks of asthma. The examination showed that he was in an asthmatic state; he appeared emaciated and dark skinned. There was marked subcutaneous emphysema about the neck, under the angles of the jaw, and over the anterior chest wall. Careful study was made to see if any crackling râles could be heard along the mediastinal border or synchronous with the heart beat, none could be determined. Electrocardiographic studies revealed only sinus tachycardia. The x-ray of his chest (Fig. 1) revealed subcutaneous emphysema that lay under the scapula, over the anterior chest wall, and along the trachea. There was none definitely visible along the mediastinal structures below the level of the bifurcation of the trachea. There was no evidence of pneumothorax on either side. The rest of the examination was consistent with his asthmatic state. His blood pressure was 110/60; the rate was 100. The abdomen revealed nothing unusual.

Intravenous glucose and aminophyllin were started and he was given oxygen by mask; also adrenalin and penicillin by injection. Within 24 hours he was definitely better and within 48 hours he required no medication except potassium iodide solution. The subcutaneous emphysema quickly subsided and he was discharged from the clinic after a 72-hour stay. When he returned in one week, a repeat x-ray (Fig. 2) was made and, as shown in the accompanying photographs, there is no evidence of subcutaneous emphysema at this time. Further questioning revealed that he had never had such an episode before. Some four years previously he had been studied by an allergist but the studies were incomplete and were never adequately followed up.

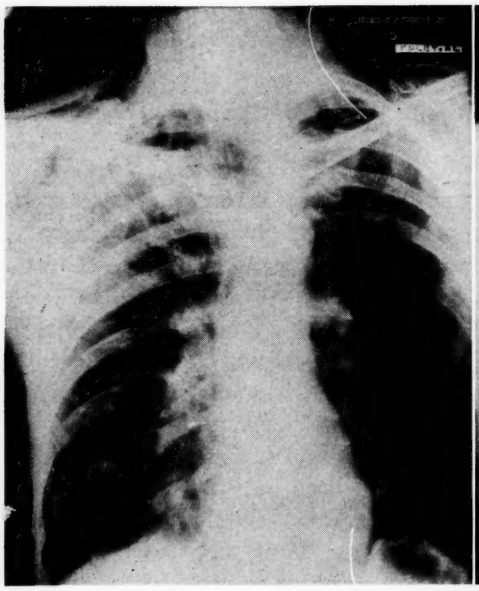

Fig. 1.

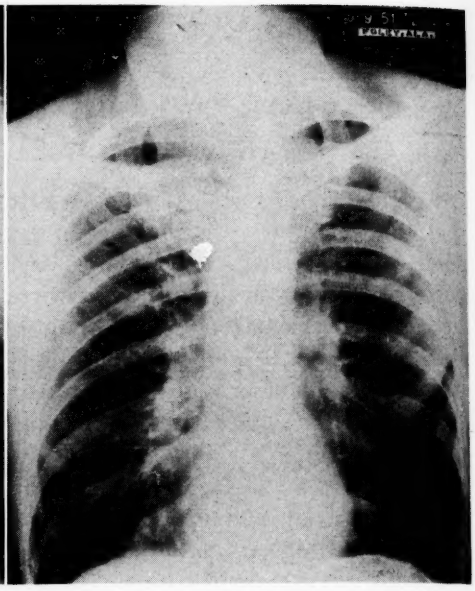

Fig. 2.

Fig. 1.—X-ray taken on 5-1-51 shows the subcutaneous emphysema underneath the scapulae and above the clavicles and along the cervical fascial planes and along the upper portion of the trachea. There is no pneumothorax. There is no evidence of emphysema along the lower mediastinal structures.

Fig. 2.—X-ray taken on 5-9-51 reveals a complete absorption of the air from the subcutaneous areas.

DISCUSSION

The interesting problem regarding subcutaneous emphysema complicating asthma is not so much the therapy but the mechanism of production. Because there was no evidence of pneumothorax in this case one could not suspect that a subpleural bleb ruptured into the pleural space. Because there was no demonstrable mediastinal emphysema, it was assumed that the leakage of air from the pulmonary tissue had been along the superior mediastinum. However, the inability to demonstrate mediastinal emphysema by x-ray was not absolutely conclusive in view of the clinical condition of the patient and his complaints. The most generally accepted theory regarding the mechanism of this complication is that an alveolus ruptures into the peri-vascular space of either a segmental or intersegmental vessel and the escaping air travels along this sheath to the hilum structures and then along the mediastinum and the cervical fascia and thus into the fascial planes over the neck and anterior chest wall. This mechanism appeared probable in this case.

Despite the fact that subcutaneous emphysema complicating an attack of asthma is rarely reported in the literature, this complication is probably more frequent because it is a complication usually disregarded by the average clinician as a minor factor. This case is being reported in order that it may be tabulated with future reviews of this subject, and stimulate the reports of others.

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THE IMPORTANCE OF HYPERPLASTIC SINUSITIS IN BACTERIAL ALLERGY*

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IN THE short period allotted to me I can hardly discuss the importance of hyperplastic sinusitis in bacterial allergy very completely. However, I shall try to present our conception of its importance on as broad a basis as possible and hope thereby to stimulate your thoughts sufficiently to convince you that bacterial allergy does exist.

I know there are many who have vague ideas about bacterial allergy and probably many who do not believe in it at all. As most of you know, our Allergy Clinic at the Roosevelt Hospital under the direction of Dr. Robert A. Cooke has been a leading exponent of bacterial allergy for years. My 20 years' contact with this clinic has convinced me that bacterial allergy is one of the most important etiologic factors in the causes of allergic manifestations.

To diagnose intelligently the etioligy of allergic diseases, it is necessary that we recognize certain criteria. In the first group, the etiologic factors may be diagnosed by skin tests, elimination diets or the history of contacts. This group includes the inhalants, ingestants and contact factors. Rackemann[1] prefers to call it the extrinsic. We prefer the term, noninfective. In this group the factors are exogenous.

In the second group, the skin tests are negative or of no importance that is demonstrable. These patients usually associate their symptoms with upper respiratory infections and not with contact inhalants or ingestants as demonstrated with skin tests. Rackemann[1] calls this group the intrinsic type but we prefer to call it the infective or bacterial type. In this group the factors are endogenous.

We may have a third group etiologically which we call the combined type. These patients have their symptoms from factors demonstrated by skin tests but in addition may have their allergic symptoms during an upper respiratory infection or from demonstrable foci of infection.

Thus, in order to make an intelligent diagnosis of the etiology of allergic diseases, me must take a careful history, do careful skin testing and make a very thorough examination of the upper respiratory tract for evidence of infections. Finally, we must evaluate these factors intelligently. In other words, a patient whose asthma appears only on contact with an animal or during the hay fever season will not be benefited by treatment of a sinus infection or the removal of nasal polyps. On the other hand, if his asthma occurs only during respiratory infections, it is not necessary to treat him with extracts of animal danders or pollens.

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It is not within the limits of my talk to discuss the immunology of bacterial allergy. We all know it cannot be demonstrated so easily as the atopic or skin-sensitive forms of allergy. While it is true that skin reactions can be obtained with some bacterial filtrates and vaccines, we cannot always evaluate their importance. On the other hand, we find that many organisms which give no skin reactions may still be important in the causation of the allergic diseases. We have seen constitutional reactions from injections of autogenous vaccines and yet no positive skin reaction was obtained on previous testing with these vaccines.

The mechanism of bacterial allergy is still controversial according to Hansen-Pruss.[2] Some investigators[3] believe that bacterial hypersensitiveness depends upon a specific antibody and that the antibodies are so closely bound to the cells that they cannot accumulate in sufficient excess in the circulation to permit passive transfer tests. Other students[4] state that a specific allergic mechanism is the basis of the delayed inflammatory reactions and that these reactions are characteristic of infectious allergies. The presence of infected tissue is then conceived to be an essential prerequisite for the production of bacterial allergy. Recent investigations[5] have shown, furthermore, that bacterial hypersensitiveness can develop in individuals who do not manifest any clinical evidence of bacterial allergy and remain apparently healthy. It is apparent then that bacterial allergy can develop from overt infections, from the absorption of bacterial substances, or from the production of bacterial products anywhere in the body.

The nature of the bacterial allergen is also a matter of argument and speculation. A workable hypothesis is perhaps that of Zinsser who stated, "Bacterial allergy is a hypersensitiveness to the somatic protein allergens of bacteria, in which the cells become sensitized by the liberation of an unchanged protein bacterial substance in the lesions."

Since my discussion is confined to the importance of hyperplastic sinusitis as an etiologic factor in allergic diseases, I will not go into any discussion of the allergic nature of this form of sinusitis. We have stated our conceptions in numerous publications[6] which may be consulted. It is the so-called thickened membrane or nonpurulent type of sinusitis and may be associated with nasal polyps. It often develops insidiously without any local symptoms and requires careful and often special methods of examination to diagnose it. I will mention these methods in my discussion of the various manifestations of allergy.

To show the importance of bacterial allergy in allergic diseases I would like to present for consideration vasomotor rhinitis, urticaria, angioneurotic edema, eczema and, lastly, bronchial asthma.

Vasomotor rhinitis is often a "bug bear" to both the otolaryngologist and the allergist. We are all accustomed to thinking of it as the classical textbook description—pale, glistening, swollen, boggy membranes which may become bluish gray in color. They are very sensitive; just the touch of cotton may produce more swelling and the outpouring of clear, watery secretion. On the other hand, the membranes may frequently be reddish and even dry in appearance.

In order to explain these various appearances of the nasal membranes, I would like to mention the diversity of opinions regarding the terminology of this disease and then discuss its etiology.

In my opinion, too many terms have been applied to vasomotor rhinitis and they are very confusing to most physicians. Allergic rhinitis is used probably most frequently. However, rhinorrhea, hyperesthetic rhinitis, atopic rhinitis, spasmodic rhinitis, hyperplastic rhinitis, atopic or allergic coryza, perennial or nonseasonal hay fever, perennial rhinitis and intumescent or hypertrophic rhinitis are all acceptable terminology.

Many physicians prefer to apply "allergic" to the rhinitis caused by extrinsic factors as demonstrated by skin tests or elimination diets and "vasomotor" to those of the intrinsic type with negative skin tests. Our studies show that the majority of this second group of patients have infection, particularly in the sinuses, and we feel that the symptoms are due to a bacterial allergy. Therefore, they can be put in the same category with the skin-sensitive types of allergy, thus using the terms allergic and vasomotor rhinitis synonomously. The clinical symptoms and rhinologic examination, including nasal smears and the pathological findings, are certainly the same in the 2 groups.

Clinically and pathologically we may say that there are 2 forms of vasomotor rhinitis, the acute and the chronic. The acute type occurs most frequently as hay fever but it is caused also by immediate reactions to inhalants, irritants such as fumes or local applications and acute infections, particularly the virus cold. The chronic form is more common and is the one caused very frequently by hyperplastic sinusitis and the inhalants. Foods are not an important factor in our experience. Cooke[7] has stated that not over 2 to 3 per cent of the symptoms of nasal allergy are caused by foods. Hansel,[8] Gay,[9] Gelfand,[10] and Spain[11] are of the same opinion. Rowe,[12] Vaughan,[13] Eyermann,[14] Walker,[15] and Tuft,[16] however, emphasize the importance of foods. In a recent analysis of 105 patients, I found foods to be unimportant.

Hansen-Pruss[2] made a very comprehensive study of nasal allergies and found that 214 or 74.8 per cent of 287 patients with allergic rhinitis had a complicating sinusitis with nasal polyps. In 93 patients suffering from perennial rhinitis he found that 61 or 64.5 per cent had sinusitis and nasal polyps.

Winkenwerder and Gay[17] observed 198 patients and found only 13 or 7.5 per cent had sinusitis, which they thought was a secondary infection. Rackemann[1] stated that in 107 patients of nonallergic etiology, 31 or 30 per cent had sinus disease, usually antral. Woodward and Swineford[18] in an analysis of 128 patients with vasomotor rhinitis found that 68 or 50 per cent had evidence of an acute, subacute or chronic sinusitis.

Thus we can see how the importance of sinusitis as an etiologic factor varies in the reports of different investigators. I think this can be explained partly by the method of diagnosis. If only anterior rhinoscopy and transillumination are used the diagnosis will be missed many times. The nasopharyngoscope should be used as small polyps or discharge posteriorly may be overlooked otherwise. This form of sinusitis may not show any darkness of the antra on

transillumination and x-rays are always necessary. If these plain films do not reveal significant change or it is not outlined clearly, films should be made after the injection of a radio-opaque solution such as Lipiodol or Umbrathor, which is a colloidal suspension of thorium dioxide. I like the Umbrathor because it gives a clearer and more delicate shadow. Kern and Schenck,[19] Kelley,[20] and Chobot[21] have shown the importance of x-rays in making a proper diagnosis of sinusitis. I would like to mention here that often a clear lavage of an antrum after the x-ray diagnosis is made does not mean there is no infection present. We believe the infection is in the deeper tissues of the membranes.

One may now ask what the treatment of these patients with vasomotor rhinitis of bacterial origin is. I would like to emphasize that any demonstrable inhalant or food allergens of either primary or secondary importance should be treated. House dust, feathers, danders, and pollens are the most most important. Some of these inhalants and the foods can be avoided. Allergies to others must be treated by injection therapy. This treatment should be carried out at regular intervals and usually over a long period of time.

In the medical treatment of the infective factors we use vaccines, both stock and autogenous. The autogenous vaccines are made from cultures of sinus washings, sinus membranes removed at operation, and swabs from the nasopharynx. This therapy also should be carried out over long periods of time. If satisfactory results are not obtained and there is sufficient pathologic change especially polyps or cysts, present, surgical procedures are necessary. These surgical procedures may also include tonsillectomy, adenoidectomy, and, I may add, submucous resection and extraction of teeth when indicated. Many otolaryngologists and allergists are prone to procrastinate operations until no benefit can be obtained. Hansen[2] in his group of 128 patients with allergic rhinitis who were operated upon found that 66.4 per cent were benefited, while in a group of 44 patients with perennial rhinitis who were operated upon 56.8 per cent were improved.

In my group of 105 patients with vasomotor rhinitis due to infection, 98 patients or 93.3 were operated upon. The operations were all performed on the sinuses except tonsillectomy in 7 patients, removal of hypertrophied membrane from the inferior turbinates in 6 patients and 1 submucous resection. The sinus operations were the removal of polyps from the ethmoids and sphenoids and Caldwell-Luc operations on the antra. The extensiveness of the operative procedures is indicated by the fact that 24 patients had a bilateral exenteration of the ethmoids for nasal polyps and a bilateral Caldwell-Luc operation.

I think poor results are often obtained by surgical measures because the surgery is not completed. Removal of polyps alone will not produce a good result if exenteration of the ethmoids and a Caldwell-Luc operation are needed; neither will doing an antrostomy if a radical antrum should be done, nor a radical antrum operation on one side if both are indicated.

The results in my series of 105 patients who were operated upon showed 20 per cent completely relieved of symptoms and 77.3 per cent definitely im-

proved as agreed upon by the patient and the physician. In this group, vaccine therapy was also used so I do not claim that surgery was the only factor in producing the improvement. We do know, however, that many patients who need sinus surgery and fail to have it done, do not do as well with their vaccine injections as those who have had their surgery completed and then take the vaccines.

One might ask here, "What about the other forms of therapy?" The use of electrocoagulation or chemical cauterization, the injection of sclerosing solutions, and x-ray therapy have not produced satisfactory results in our patients and some have been harmed, especially with chemical or electrical cauterization. Submucosal electrocoagulation as advocated by Weille[22] has been helpful.

The use of the antihistamine drugs has given temporary benefit to many patients with the skin-sensitive types of allergy but the infective group has not been helped very much since the side reactions are often so unpleasant many patients have stopped the drugs voluntarily.

The antibiotics from sulfonamides to terramycin have been used extensively. Of course, they have had no effect on the skin-sensitive group but the infective group has been helped if there is pus present and the organism is sensitive to the particular antibiotic being used. Since most of these patients have the nonpurulent type of sinusitis the results have been disappointing except when there has been an upper respiratory infection and a secondary suppurative reaction is present. Side reactions are also important in the use of antibiotics.

Cortisone and ACTH have been used on a small number of patients but the results have been disappointing in that the relief is only temporary. Polyps decrease in size quickly and practically disappear, but shortly after the drug is discontinued they reappear.

In discussing urticaria, angioneurotic edema and eczema as seen in the allergic patient, we may say that the etiology is the same as with vasomotor rhinitis. In other words, the causative factor may be (1) an allergen demonstrated by skin tests or elimination diets; (2) an infection, or (3) a combination of the other 2 groups of causes. The first group is usually diagnosed very easily by a careful history regarding foods and contacts and the proper skin tests. The second or infective group is usually more difficult to diagnose and also to treat.

Since the form of sinus disease present in the infective group is most often a polyp or cyst in the antrum, transillumination of the sinuses is not worth much and x-rays are always necessary. In many patients one must resort to the injection of Lipiodol or Umbrathor to make a proper diagnosis.

Fink and Gay[23] have made a comprehensive study of 170 patients with urticaria and angioneurotic edema and found that the group with focal infections made up the greatest number (52 patients or 30 per cent). Sinusitis was present in 9 patients which, I think, is much too small a number if the patients are studied thoroughly with x-rays. The history is also important in this group in that they will very often tell you that their symptoms are much worse after colds or sore throats.

The conservative treatment of this group with vaccines, both stock and autogenous, will help a good many patients but surgical procedures are necessary eventually in a large number. The same completeness of operations as described in the surgical treatment of vasomotor rhinitis is necessary if the best results are to be obtained. Fink and Gay[23] reported 74 per cent cured with 12 per cent improved in their group of 170 patients in whom focal infections were removed. I might add that they followed their patients from 2 to 10 years.

We have observed that many patients do well only temporarily after a sinus operation because foci are often present in the tonsils, adenoids or teeth and these should be removed to obtain the best results.

The use of the antihistamines, antibiotics and cortisone in these bacterial cases has been helpful but the relief is temporary.

Before discussing bronchial asthma as caused by hyperplastic sinusitis, I would like to state that 2 other manifestations of allergy, hay fever and migraine, are affected by hyperplastic sinusitis in only a secondary manner. Bad results in the treatment of hay fever with injections may be due to a complicating sinusitis which should also be treated. I have never seen a true migraine result from sinusitis but an associated sinusitis may produce intermittent headaches in a patient with migraine and proper treatment is required.

As stated previously in the discussion of vasomotor rhinitis, asthma is the one allergic manifestation that is associated very importantly with hyperplastic sinusitis. Many allergists and otolaryngologists are undecided whether sinusitis is the cause of asthma or asthma is the cause of sinusitis. Such allergists as Rackemann[1] and Gay[9] are undecided about the exact etiologic significance of sinusitis as a cause of asthma. We, however, are very definitely of the opinion that sinusitis may be the primary or secondary cause of asthma.

You are familiar with the pathology, bacteriology and diagnosis so I will not go into additional detail. I want, however, to show the incidence of sinusitis in asthmatic patients and to discuss the results of the treatment of the sinusitis as far as the effect on the asthma.

The incidence of sinusitis in asthma patients as reported in the literature varies. One reason for this is the method of diagnosis of the sinusitis. If it is diagnosed by rhinoscopy alone the incidence is low. If it is diagnosed with x-rays the incidence is higher. Gottlieb[24] found sinusitis present in only 26 per cent of 117 patients with asthma. Kern and Schenck[19] after a careful study of 400 cases of asthma found that 70 per cent had clinical evidence of sinusitis and 87.5 per cent showed x-ray evidence of disease. Kelley[20] reported that 89 per cent of 100 patients with asthma had rhinologic and x-ray evidence of sinusitis.

The most comprehensive study of the incidence of sinusitis as a cause of asthma was reported by Cooke.[25] He analyzed 688 cases of asthma and found sinusitis to be the cause of the asthma in 39 per cent of 257 cases with the asthma beginning between 10 and 30 years of age; 65 per cent of 171 cases between 30 and 50 years; and in 83 per cent of 42 cases after 50 years. Excluding children in the first decade of life in whom the tonsils, adenoids and

the lymphoid tissue of the pharynx are more important, he found that sinusitis was the only cause of the asthma in 45 per cent of 470 patients. As a contributing factor it was an additional cause in 15 per cent.

Cooke in his study of the group of 688 cases with asthma also found that there was a positive antecedent history of allergy in 45 per cent of the entire infective group and 52 per cent of the skin-sensitive group. Sixty-six per cent of 195 cases of asthma gave an antecedent history of asthma and there were other allergic manifestations in 34 per cent.

Maxillary sinusitis is the most frequent type of sinusitis found and ethmoidal, the second. Frontal sinusitis is the least frequent. In a study of 163 patients, maxillary sinusitis was present unilaterally in 44 patients and bilaterally in 108, while ethmoidal sinusitis was present in 40 unilaterally and 98 bilaterally. This study shows how frequently the sinusitis is bilateral, and I might add that pansinusitis is present in a high percentage.

We are now at the stage where we may ask, "What is the treatment of this sinusitis and what are the results?" The medical treatment, so to speak, is not very important in hyperplastic sinusitis. Irrigations are done for cultures and if there is a suppurative exacerbation the use of antibiotic preparations is helpful in the acute exacerbations. But for the treatment of chronic hyperplastic sinusitis they are of very little value.

The treatment of the hyperplastic sinusitis when it has reached the proper stage is operative. When I say operative treatment I mean the complete removal of the infected tissues. A simple polypectomy or the "window" resection of the antrum seldom suffices. When removing nasal polyps the underlying infected membranes in the ethmoids or sphenoids must also be removed and the removal of the diseased membrane in the antrum requires a radical operation. Submucous resection and turbinectomy are worth very little in producing any permanent improvement in the asthma.

We have always maintained that the complete operative removal of this hyperplastic membrane is necessary if a good result is to be obtained with the asthma. Gay[9] in his recent book on asthma has taken the same attitude.

In the previously quoted group of 163 patients with asthma, I did an ethmoidectomy unilaterally on 34 patients and bilaterally on 91, and a unilateral Caldwell-Luc operation on 37 patients and a bilateral on 64 patients.

Gay[9] analyzed 125 patients with asthma whose sinuses had been operated on at the Johns Hopkins Hospital. The longest postoperative period was 20 years and the shortest, 2 years. Twenty-four patients (19.2 per cent) reported complete relief; 26 cases (20.8 per cent) reported infrequent attacks of asthma, occurring especially when they carelessly exposed themselves to inclement weather conditions; 17 cases (13.6 per cent) reported recurring attacks but not so severe as before operation; 5 cases (4.0 per cent) reported questionable relief; and 53 patients (42.4 per cent) reported no relief whatever. Unfortunately, in his report Gay did not give any information as to the associated allergies in his group of poor results nor the completeness of operative removal of diseased sinus membranes. He stated, however, that 71 patients had recurring

sinus symptoms subsequent to their operations. In the main these failures respecting sinusitis included the 53 (42.4 per cent) of the reported failures in asthma.

It seems to me from a study of these reports that there are reasons to explain the discouraging results. In the first place the importance of associated sensitizations is often not made clear, nor, in the second place, how completely the diseased sinus membranes were removed, that is, whether all the sinuses were operated upon or isolated ones only. We have always maintained that this critical analysis of operative results is necessary.

Since 1935 we have made six very complete studies of the results of sinus surgery on patients with asthma. The first study[26] reported in 1935 included 120 cases, the earliest of whom had been followed for 3½ years postoperatively. The most recent study[27] included 200 cases which were followed postoperatively from 6 months to 17 years. Our results have shown 70 per cent, or slightly less, improved in all the 5 previous studies and the sixth showed 69 per cent. We have not included the first 6 postoperative months because the results noted then are too transitory. The anesthetic produces temporary relief from the asthma in some patients, while in others the removal of the infected sinus membranes may produce immediate exacerbation of the asthmatic symptoms.

I have divided the operative group for comparison, first, into the types of asthma (i.e., purely infective or infective plus associated sensitizations) and, second, into those in whom isolated operations or incomplete surgery has been done.

The symbols +, ++, and +++ have been selected arbitrarily to designate the improvement in the asthma. One plus signifies slight improvement in asthma, no improvement or even worsening; 2 plus designates improvement as agreed upon by the patient and the physician; 3 plus no asthma or a rare attack. The improvement in the whole group is expressed as the sum total of the 2 plus and 3 plus results or 69 per cent. This is about the same as those reported in our 3 previous surveys and in Cooke's book on allergy.[27]

The infective group comprised 107 cases and the combined group, that is infection plus sensitizations, 93 cases. The group completely operated on comprised 146 patients and the incomplete group 54 patients. It was obvious that the group completely operated on showed a much higher percentage of improvement (79.9 per cent) than the group incompletely operated on (35.2 per cent). I would like to add here that 27 patients who had had a "window" resection or antrotomy showed only 40 per cent improvement with their asthma. Nineteen of these patients subsequently had a radical antrum operation and 79 per cent showed improvement with their asthma later.

It should be noted that, in the group completely operated upon, the incidence of improvement is greater with the longer postoperative periods. I believe that this may be explained by the fact that there are secondary foci in the cervical and bronchial lymphatic glands and in the bronchial mucosa. These secondary foci heal slowly. It is possible that the patients who did well immediately after operation and remained well never had these secondary foci.

On the other hand, the patients who did not do well, even as the postoperative period increased, may have lacked the capacity to overcome these foci.

It is seen that the results are better in the combined type of asthma than in the infective type. In the former group the infection is often a secondary factor and in addition all these patients were treated with injections of the indicated allergens as well as by the elimination of the allergens when possible. I think the injections of house dust in the proper patients has helped to maintain prolonged freedom from asthma and at the same time helped to prevent the occurrence of nasal polyps. Practically all the patients in the infective and combined groups have been given injections of vaccines made from cultures of the infected sinus membranes removed at operation. In addition, all those with extranasal infections such as molds and spirochetes have been treated, and infected teeth, tonsils and adenoids have been removed.

I have also studied this entire group of patients from the standpoints of age at onset of the asthma, duration of the asthma, and age at operation. In a total of 52 patients in the 3 plus group only 7 (13.4 per cent) developed their asthma before 21 years of age, while in the 1 plus group of 64 cases there were 21 such patients (32.8 per cent). The greatest number of patients in the 3 plus group developed their asthma between the ages of 21 and 35 years; there was another peak from 50 to 55 years.

As far as duration of asthma is concerned, of 46 of our 3 plus patients practically 50 per cent had had their asthma less than 5 years, while an additional 25 per cent had had their asthma not more than 6 to 10 years. Of 60 patients in the 1 plus group, 40 per cent had their asthma for 5 years or less and 60 per cent for 10 years or less.

An analysis of the group from the standpoint of age at operation showed that of 46 patients in the 3 plus group 76 per cent were between the ages of 31 and 50 years. Of 62 patients in the 1 plus group 31 per cent were between the ages of 20 and 35 years and 34 per cent between 35 and 50 years.

SUMMARY

Hyperplastic sinusitis is a very important etiologic factor, either primary or secondary, in such allergic diseases as vasomotor rhinitis, urticaria, angioneurotic edema, eczema and bronchial asthma.

It is necessary that a proper diagnosis of the etiology of the allergic disease be made. These factors may be classified as: (1) skin sensitive or noninfective; (2) infective or bacterial and (3) combined (infection plus sensitizations).

One hundred and five patients with vasomotor rhinitis and evidence of hyperplastic sinusitis were studied from an etiologic standpoint. Only 25 per cent of them showed skin sensitizations of importance. Foods were definitely unimportant.

An analysis of the postoperative results obtained by surgical procedures on 200 asthmatic patients has been presented. Sixty-nine per cent of the total group showed complete or definite relief of their asthma. The group who had

their pathology removed completely showed the greatest improvement. The ones who had associated sensitizations showed 16.4 per cent more improvement than the ones with infection alone.

It is emphasized that to obtain the best results with sinus surgery any associated infections such as those of the tonsils, adenoids and teeth should be eliminated and any etiologic sensitizations should be treated.

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Editorials

THE INTERNATIONAL ASSOCIATION OF ALLERGOLOGY

As medical knowledge rapidly becomes more complex and specialized, free exchange of information and ideas between those working in the field is increasingly important for further progress. The accomplishments of a physician devoting his efforts to a narrowly specialized branch of medicine grow in proportion as he makes his knowledge an integrated part of that amassed by colleagues studying the same field in other parts of the world and also those working in other branches of medical science. The techniques of allergic diagnosis and treatment of disease have been developed to a remarkable degree in the United States, and large clinics have been established in the chief cities for the utilization of these methods, setting a high standard for the practical management of allergic diseases. One might think that these great clinics would be the sources of any noteworthy advances in the field of allergy. While they have been active in research, and made real contributions to its growth, a surprising number of the fundamental principles upon which the field of allergy is based have come from chemists, physiologists, pathologists, and pharmacologists who have never treated a patient with hay fever, and who are geographically far removed from the main centers of allergic therapy. The entire concept of the role of histamine in allergy and the possibility of producing pharmacologic antagonists to it, may be mentioned as one example.

This need for expanding contacts is reflected in the growth and activities of allergy societies. The first organized group in the field, the Association for the Study of Asthma and Allied Conditions, began twenty-eight years ago with twelve members, all from the eastern United States. Now each of the two great national allergy societies in America has several hundred members and there are a dozen or more local and regional organizations. In recent years allergy societies have been organized in Canada, South America, and Europe. Through associate memberships and guest lecturers, there has been some interchange of ideas between these many organizations.

Through the initiative and industry of Dr. Fredrick W. Wittich, these are now formally linked in an international union, the International Association of Allergology. The First International Congress of the Association held in Zurich, September 23-29, 1951, marked the beginning of a new era in allergy. The program was broadly conceived, both geographically and medically, with outstanding speakers from all parts of the world and all branches of medical science bearing on the pathogenesis, diagnosis, and treatment of allergic disease. As indicated in the report of Dr. Howard Osgood which follows, the Congress was entirely successful, with delegates from all important allergy societies and the principal nations of the free world. Never before has a single meeting offered so much to the student of allergy, whether he be primarily interested in the practice or in the pathoolgy and physiology of allergic disease.

Aside from its scientific interest, the Congress offered the opportunity to place the Association on a firm basis as a permanent world-wide organization to advance the study of allergy. This will not replace the various national and local allergy societies, but will rather strengthen them by a free interchange of information and ideas. The Association merits the support of all allergy societies and allergists. Dr. Wittich is to be congratulated for his vision in planning the organization and his work in bringing it to reality.

W. B. SHERMAN, M.D.

REPORT OF THE AMERICAN ACADEMY OF ALLERGY COMMITTEE FOR THE FIRST INTERNATIONAL CONGRESS OF ALLERGY, ZURICH, SWITZERLAND, AND THE INTERNATIONAL ASSOCIATION OF ALLERGOLOGY

The First International Congress in the field of allergy was held in Zurich, Switzerland, September 23 to 29, 1951, under the combined auspices of the International Association of Allergology, initiated several years ago by Dr. Fred W. Wittich of Minneapolis, the Swiss Federal Council, the governments of the Canton and of the City of Zurich, the University of Zurich, and of several national and local Swiss medical societies. Its honorary president was Dr. h. c. PH. Etter, Head of the Swiss Department of the Interior (its president was Dr. Ch. W. Loeffler, Professor in the Hygiene Institute of the University of Zurich, and president of the Swiss Allergy Society). Attending the Congress were physicians from thirty-nine nations of five continents, including those from such distant lands as Indonesia, Persia, India, and South Africa. The total registration of physicians and guests was about six hundred. Over thirty members of the American Academy of Allergy, including foreign members, were in attendance in Zurich. Brazil sent a delegation of nine or ten doctors. Official delegations were sent by many national governments, including one appointed by the Division of International Conferences, U. S. Department of State, and headed by Dr. Arthur Stull of the Office of the Surgeon General of the Army.

The scientific assembly met from Monday, September 24, to Saturday noon, September 29, with the papers grouped under eight major topics. The morning sessions were given over to presentations up to forty-five minutes in length. During the afternoons, three sessions were held simultaneously at which many short reports were read. Altogether nearly 150 papers were given. Among the leaders on the program from the United States were Dr. A. R. Rich of Baltimore, and Dr. M. G. Bohrod of Rochester, N. Y.

Although the speakers were privileged to use the language of their choice, French, German, and English were the most used. The large contingent from the English-speaking nations appreciated the courtesy of the many nationals in using English so frequently.

The Swiss doctors and others on the local committees did a magnificent job in arranging hotel accommodations and in carrying out the innumerable details for the scientific meetings and for the entertainment. To Prof. A. S.

Grumbach of Zurich, Secretary General of the Congress, go the cordial thanks of everyone for his ready skill in meeting all situations arising during the week, and for his unfailing courtesy and good humor.

A reception was held in the Zurich Congress House on Sunday evening, September 23, following the formal opening of the Congress. An evening party was held on Tuesday at the Dolder Grand Hotel. On Thursday, about three hundred doctors made an all-day excursion by motor bus to Basel. There an excellent scientific program was presented in the auditorium of the University of Basel. After lunch, visits were made to the pharmaceutical plants of Ciba, Hoffman-La Loche, and Sandoz. The research departments of these companies had many experimental demonstrations in progress, which were ably explained by their chiefs of research.

The official banquet was held on Friday, Prof. Loeffler presiding. Prof. Grumbach made a brief speech in English, which he then repeated in German, French, Italian, and Spanish. Entertainment was provided by an orchestra and by an excellent Swiss Männerchor which included some very fine yodlers. An unusual feature was a performance by a flag juggler, who did extraordinary and beautiful things with a large silk Swiss flag on a short staff.

Simultaneously with the scientific sessions, organizational meetings were held throughout the week to establish the International Allergy Association. Thirty national allergy societies had indicated their official affiliation with the proposed international association. These societies were: The American Academy of Allergy, American College of Allergists, American Society of Ophthalmologic and Otolaryngologic Allergy, Argentine Association of Allergy and Immunology, Argentine Allergy Society, Section on Allergy of the Australian Medical Society; and the Allergy Societies of Belgium, Brazil, Canada, Chile, Colombia, Cuba, Denmark, Finland, France, Germany, Great Britain, Hungary, Israel, Italy, Japan, Mexico, The Netherlands, Peru, Portugal, South Africa, Spain, Sweden, Switzerland, and Uruguay. For the Academy, President Baldwin had appointed Dr. F. M. Rackemann as its voting representative in the I. A. A., Dr. S. M. Feinberg as member of the Committee on the Constitution and By-laws and Dr. H. Osgood on the Committee on Nomenclature. These three men, acting jointly as the "Zurich Committee" of the Academy, took active parts in the organization of the I. A. A.

The above two Committees of the nascent I. A. A., both composed of one representative from each affiliated national allergy society, first met on Saturday and Sunday preceding the scientific sessions. Each large committee then appointed a working committee of five members, in which the respective Academy members were included.

By intensive work over several weeks preceding the Congress, Dr. Feinberg had drawn up a full draft of a tentative constitution and by-laws, in which were correlated the proposals previously presented by Dr. Wittich and the Academy's International Committee, by Dr. Rackemann, by the British Association of Allergists, and by Dr. A. S. Grumbach. A French translation of this document was made and both the English and French versions were mimeographed and taken to Zurich to form a basis for discussion. By hard work and frequent meetings, the working committee on the constitution had a

draft ready by Wednesday to present to the Committee on the Constitution. The full committee, after reviewing it, presented this draft at the meeting of the voting representatives of all the affiliated societies held on Thursday evening. These voting representatives sat from 9:30 P.M. to 2 A.M. At this session a definitive version of the Constitution and By-laws, in English, was adopted and signed by each representative. Copies of this Constitution and By-laws, after minor corrections, will be sent to every affiliated society. Considering the diversity of languages and ideas involved, this document may be considered an achievement in international cooperation.

Summarizing briefly the essential points: The name of the association will be The International Association of Allergology. Membership will be by national allergy societies, with provision for individual membership from countries where no such society exists. Voting members of the affiliated societies automatically become members of the I. A. A.

The governing body of the I. A. A. will be a House of Delegates. Each member society (thirty at present) will elect one Delegate to this House of Delegates for a term of four years. An International Congress will be held every four years, at which time the House of Delegates will also meet in regular session.

The officers of the I. A. A. will be seven in number: President, President-Elect, First, Second and Third Vice-Presidents, Secretary General, and Treasurer. The First Vice-President shall be from the country in which the next Congress will be held.

The business of the International Association of Allergology between Congresses will be carried on by an Executive Committee of twelve members. These will consist of the seven officers, the Past-President (for one term of four years), and four members-at-large elected by the House of Delegates.

Nominations for officers and for members-at-large of the Executive Committee will be made by a nominating committee of twelve Delegates: 3 from Europe, 3 from North America, 3 from Central and South America (including Cuba) and 3 at large. Nominations may also be made from the floor at the regular meeting of the House of Delegates.

Election of officers and members of the Executive Committee will be by majority vote of the House of Delegates in regular meeting assembled.

Dues will be paid only by member societies and by individual members from countries where there are no allergy societies. The amount of the dues will be determined by the Executive Committee assisted by a Finance Committee. (End of Constitution.)

The Committee on Nomenclature, after considering suggestions submitted by the Argentine Allergy Society and The Netherlands Allergy Society, and following a report by its working committee, recognized the need for arriving at generally accepted definitions for many words and terms used in connection with allergy, and for establishing equivalents in the scientific languages of the world. This work will necessarily require considerable time and will continue between Congresses. The Committee on Nomenclature therefore recommended that a small committee be appointed with an executive secretary, and that funds be provided for the correspondence involved. No action in this

matter was taken in Zurich, and the question will have to be decided by the Executive Committee.

No official journal was established by the delegates in Zurich. The papers presented at each Congress will probably be published in a "Proceedings."

Following nominations made by a nominating committee composed as prescribed by the new Constitution, the voting representatives (Delegates) of the member societies, meeting in the long session on Thursday night, elected the following officers and members-at-large of the Executive Committee. These will serve until the end of the Congress in 1955.

President:	F. W. Wittich, U. S. A.
President-elect:	S. M. Feinberg, U. S. A.
1st Vice-President:	U. Fabiano Alves, Brazil
2nd Vice-President:	P. Vallery-Radot, France
3rd Vice-President:	D. A. Williams, Great Britain
Secretary General:	B. N. Halpern, France
Treasurer:	A. S. Grumbach, Switzerland

Members-at-large on Executive Committee:

Ch. W. Loeffler, Switzerland
Egon Bruun, Denmark
F. M. Rackemann, U. S. A.
M. Salazar Mallen, Mexico
E. A. Brown, U. S. A.

Although the United States appears to have an undue number of representatives among the officers and members of the Executive Committee, the very large membership in the American allergy societies was taken into consideration, and the ratio may vary in future years.

The next International Congress of Allergology, on the invitation of the large Brazilian delegation at Zurich, was voted to be held in Rio de Janeiro in 1955.

In conclusion, your reporter would like to stress the cordial relations which developed during the Congress among the individuals from the thirty-nine nations. Many new and useful ideas were presented in the scientific sessions. But of equal importance, and a source of much pleasure, were the opportunities for informal conversations and personal friendships afforded by this international gathering. These contacts will bear fruit through the years. Those who were in Zurich will look forward eagerly to their renewal in Rio de Janeiro in 1955.

The International Association of Allergology, which Dr. Wittich has worked hard to establish, has the support of the national allergy societies of the world. Its permanence and stability is assured by the unity achieved in Zurich. The Association will, from now on, be a powerful force in advancing and disseminating the knowledge of allergy among the civilized nations.

Howard Osgood, Chairman,
International Committee of the American
Academy of Allergy.

FEDERAL STANDARD FOR WHITE BREAD

After extensive hearings in which several members of The Academy of Allergy took part, the Federal Food and Drug Administration issued tentative standards for the ingredients of white bread. The ingredients, other than the wheat flour and yeast, which may be included, are of interest to practicing allergists.

This is a brief abstract of the proposed standards contained in the notice of a tentative order on bread products which appeared in the Federal Register of Aug. 8, 1950.

Bread standards, as proposed in the tentative order of the Federal Security Administration, establish, under the authority of the Food, Drug, and Cosmetic Act, regulations for controlling the identity, ingredients, manufacturing, and labeling of bakery products. Since the word "bread" standing alone is a synonym for "white bread" in both trade and consumer understanding, the proposed standard for bread is designed to represent one product only—that which consumers have regarded for generations as the bread made in the home from plain white flour, water, and yeast, usually with salt and shortening, and somewhat modified in modern times in the commercial bakeries where a number of minor ingredients now considered necessary in mechanical baking operations have been added. Any other product, the ingredients of which would legally prevent its promotion under the label "bread" or "white bread," such as rye, pumpernickel, or wheat-and-soy bread, is not covered by the tentative order.

To clarify the issue concerning both color and nutrition, it should be remembered that in bread white is more than a color; it is a fixed idea in the mind of the consumer. While enriched bread, for which a proposed standard is also provided, is similar in color to white bread, the Food and Drug Administration believes it differs sufficiently from white bread to warrant distinguishing it as a separate product. Milk bread, too, is unmistakably white in color, but its contents are also such as to justify a separate proposed standard.

Consumers normally expect white bread and rolls to be made principally with wheat flour. Factual findings indicate, however, that during times of wheat scarcity, such grain products as corn flour have been extensively used to replace small amounts of wheat flour. Potato mash is sometimes used to develop a preliminary yeast growth which is then incorporated in the dough. Optional flour ingredients have been universally used by commercial bakers who find that dusting flours, frequently consisting of products other than wheat flour, are necessary to keep dough from sticking to receptacles and machinery. Although much of the dusting flour is incorporated in the dough, amounts no greater than 3 parts of the foreign substance to 100 parts of wheat flour produce a loaf conforming to the normal expectation of present-day consumers, and are, therefore, permitted under the standards.

The propriety of replacing wheat flour by not more than 3 per cent of "other edible farinaceous substances" has been recognized since 1923, when the advisory standards for white bread, issued by the Secretary of Agriculture, made their first appearance. After the bread hearing in 1941, bakers who had experimented with soy flour found that they could use up to 3 parts in 100 parts of flour "without a substantial change in the physical characteristics of white bread." Many bakers now wish to have soy flour recognized as an optional ingredient within this limit, and the proposed order contains such recognition. Bakers using more than this amount of soy flour do so primarily because they wish to increase the content and quality of protein in their product. As the proportion of soy flour exceeds 3 per cent, the taste and color of a loaf are progressively changed. While products known as wheat-and-soy breads have been sold with varying proportions of the named ingredients, no bakers have expressed an interest in the adoption of a standard for wheat-and-soy bread. Since no standards have been proposed for wheat-and-soy bread or other nonstandardized products such as rye and pumpernickel bread, adoption of the order under discussion will have no effect upon them.

The type of inactive dry yeast which is used to impart a homemade flavor adversely affects the color of bread when more than 2 parts of such yeast to 100 parts by weight of flour are used. The tentative order therefore limits the amount of inactive yeast to that which good baking practice has not previously tended to exceed.

Shortening, which is commonly added to dough, may consist of any food fat or food oil, including butter, oleomargarine, cream, or any mixture of these. Then action of shortening is sometimes accentuated by substances derived from corn oil or soybean oil, or by glycerinated fats (referred to in the proposed order as mono- and diglycerides of fat-forming fatty acids). This is a legitimate practice. Prior to 1942, the specified fatty acid derivatives were used in amounts usually not greater than 5 per cent in many types of shortening, but since 1942 it has been shown that their use in even greater proportions still further increases the shortening effect. The proposed standards limit the use of such substances to 25 per cent of the shortening content.

Milk is composed of water, milk fat, and other components commonly known as nonfat milk solids. The nonfat milk solids include proteins, milk sugar, various minerals, and certain water-soluble vitamins. In their dry form these solids have been an important commercial bread ingredient, but during, and shortly after, World War II they were not available in sufficient quantities. As a substitute, manufacturers of dairy products developed a dried cheese whey which, prepared from proper raw materials, is suitable for human food. Although cheese whey, containing more lactose and less protein, imparts properties not identical with those produced by nonfat dry milk solids, it is acceptable in its performance of certain desirable functions in bread.

To promote uniformity in day-by-day bakery operations, it has become a widespread practice among bakers to add to their dough small quantities of harmless mineral salts which are supposed to stimulate the growth of yeast during fermentation. Other salts, known as oxidizing agents, do have an effect upon the fermentation process. These ingredients are commonly known as yeast foods, dough conditioners, and bread improvers. Since their use tends to lessen variabilities in dough quality resulting from differences in flour characteristics, water supply, and other factors, mechanized handling is facilitated. The proposed standards recognize such usage but point out that it is not necessary to use more than 0.25 part of the mineral salts or 0.0075 part of the oxidizing salts to 100 parts of flour.

Old bread is harder than fresh bread, its taste has changed, and it is almost universally regarded as less desirable. The common practice of many bakers is to withdraw bread from sale 2 days after baking; the price is frequently reduced on bread more than one day old. After the issuance, in 1943, of the first proposed standards, it was discovered that the addition to bread dough of small amount of substances known as emulsifying or surface-active agents caused the resulting product to be more compressible and to feel softer when squeezed. Three classes of compounds containing one or more of these substances were subsequently offered for sale to bakers. The first 2, under the trade names of Spans and Tweens, had earlier been promoted among manufacturers in special mixtures purporting to be egg substitutes. The third, introduced in 1947 and known principally under the trade names of Myrj 45 and Sta-Soft, became the most generally used. Some bakers using the newest compounds advertised softness as an index to the freshness of their bread. None advised consumers by label statement or advertisement concerning the use of this chemical. Since softness and freshness are intimately connected in the minds of bread purchasers, many consumers were doubtless led to believe that bread containing surface-active ingredients was not as old as it actually was. Even more important, there was no conclusive evidence that these substances would be safe when consumed over a long period of time. The tentative order does not authorize the use of such emulsifiers or softeners.

A widespread practice, especially during the summer months when mold development on bread is most rapid, has been to add retarding substances. The tentative order recognizes for this purpose sodium and calcium propionates and sodium diacetate. The rope-forming bacterium, characterized in advanced stages by an unpleasant odor and a pasty consistency in the center of the loaf, can survive the temperature of baking in its spore form. It has been found that increased acidity is effective in preventing the development of this organism. A pint of 100 grain vinegar for each 100 pounds of flour used in the dough has proved effective. The substances recognized for retarding mold have also been found effective against the growth of the rope-forming organism. In neither use, however, will the propionates exceed 0.32 part, or the sodium diacetate 0.04 part, to 100 parts of flour.

Announcement

RESEARCH FELLOWSHIP IN PEDIATRIC ALLERGY

Under the direction of Dr. Bret Ratner in the Departments of Pediatrics and Immunology, New York Medical College, 106th Street and Fifth Avenue, New York 29, N. Y.

These Fellowships are full time. One started July 1, 1951, the other starts January 1, 1952. Applicants must be certified in Pediatrics or have the requirements for certification. The Fellowship runs from one to two years and will consist of intensive training in Immunology and Animal Research pertaining to the field of hypersensitiveness; intensive study of allergic children, which will include skin testing, laboratory work, clinical follow-up, as well as clinical research. Applicants who have had previous training in Chemistry and/or Immunology and who are desirous of a research career will have preference.

Book Reviews

Pediatric Allergy. By Robert Chobert, M.D., New York, 1951. McGraw Hill, 284 pp., $4.50.

Based on years of experience in a large pediatric allergy clinic, this book offers simple, practical advice on the diagnosis and treatment of allergic diseases of infants and children. The theoretical background is handled briefly and complete details are given for diagnostic and therapeutic procedures.

In a field where sharply divergent views are held by different writers, the author frankly states his own opinion and supports it with illustrative case histories presented briefly. Obviously some will disagree with him.

The role of infection in the causation of asthma and dermatitis in children is emphasized; the role of foods is recognized but less stressed. The material on infantile eczema reflects the persistent confusion about etiologic factors and, as such, leaves the beginner with only a vague idea of specific treatment. The sections on symptomatic treatment are well done.

On the whole it will prove a useful guide to the pediatrician desiring aid in handling allergic diseases.

Allergy in Relation to Pediatrics. Edited by Bret Ratner, M.D., St. Paul & Minneapolis, 1951. Bruce Publishing Co. 228 pps. $3.75.

Compared to the internist, the pediatrician enjoys a most favorable position in the treatment of allergic disease. His patients usually present earlier and less complicated stages of diseases, their environmental contacts and diets are less complex, the response to proper allergic managements is better, and the chances of spontaneous loss of specific sensitization is greater. He also has more opportunity to observe the genesis and evolution of allergic manifestations and a better possibility of attempting prophylactic measures. For these reasons, the pediatric field is a most important part of allergy and much depends on the awareness of pediatricians and general practitioners of the potentialities of allergic handling in this age group. The present volume, a panel discussion of the American College of Allergists, with the assistance of members of the American Academy of

Pediatrics, reviews the present status of the problem. It should be of value in acquainting physicians, whose primary interest is in general pediatrics or in general allergy, with the methods and results of those who are devoting a major portion of their efforts to pediatric allergy.

Consisting of chapters on various aspects of the field, by seventeen widely known contributors, the volume is not easily described in generalization and space does not permit review here of each separate chapter. Many of the papers are outstanding reviews of difficult subjects. Those of William P. Buffum on asthma in infancy, of Louis Webb Hill on the significance of skin tests, Susan Dees on neurological allergy, and Jerome Glaser on the office management of the allergic child are a few of the most noteworthy.

As a panel discussion, the book lacks certain features which would make it of value as a text or reference book for the practical use of those needing instruction in the field. Most important aspects are covered, with the notable exception of the commonest allergic disease of childhood — dermatitis venenata. The lack of an index hampers the use of the volume for reference. As might be expected in a panel discussion there is considerable overlapping of various papers and when this occurs differences of opinion between the authors are occasionally apparent, some of which may confuse the reader to whom the subject is relatively new. For example, the author of three different chapters disagree on the fundamental point of what constitutes asthma. In discussing skin tests on infants, one author states that their skin reacts poorly and usually shows few and small positive reactions, while another particularly stresses the point that children at any age react to skin tests more easily than do adults.

Discussions of the genesis and possible prophylaxis of allergic disease form an important part of the book. The chapter on the genesis of allergy, in emphasizing the importance of exposure in the development of sensitization, greatly minimizes the influence of heredity. Yet, as becomes apparent in other chapters, recognition of the hereditary factor is one of the symptoms of prophylaxis. The measures proposed to avoid sensitizing contacts, namely restrictions of the diets of pregnant and nursing women as well as control of both diet and environment of the potentially allergic child, are so rigorous as to be impractical of application to all women and infants, but such measures may prove valuable in those families where the presence of a strong hereditary tendency to allergy supplies the indication for instituting such a program.

It is regrettable that a book containing so much valuable material is impaired by the devotion of considerable space to old controversies such as that of scratch versus intracutaneous skin tests. At present probably all allergists who elect to use the intracutaneous test as a routine will agree that the scratch test is safer, but they will not accept the preposterous statement of one of the contributors that in spite of all modern precautions, intracutaneous testing continues to produce general reactions in 2 per cent of all patients tested. In support of this appraisal of the current situation the author offers two references, the most recent 24 years old. Such uncritical prejudice is unfair to the other contributors who have devoted time and thought to the preparation of their chapters.

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